

CLINICAL RESEARCH PROJECT

Protocol #: 19-H-
Drug Names: Ibrutinib, Duvelisib
IND: exempt

Title: Duvelisib for Ibrutinib-Resistant Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Short Title: Duvelisib for Ibrutinib-Resistant CLL

Keywords: Duvelisib, PI3K Inhibitor, Ibrutinib, BTK Inhibitor, CLL, SLL

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301-402-1806

Bldg 10, CRC 3-5132

Subjects of Study:

Number

Sex

Age-range

33 evaluable

M/F

≥18

(Accrual Ceiling 36, to account for ineligible subjects)

PROTOCOL SUMMARY

SYNOPSIS

Background:

- In chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), ibrutinib resistance is predominantly caused by somatic mutations in *BTK* and *PLCG2*.¹⁻³ Virtually all patients with detectable mutations eventually develop progressive disease.^{2,4} Patients who discontinue ibrutinib often have rapidly progressive disease that can be difficult to control.⁵ These observations suggest that BTK inhibitors still exert at least a partial anti-tumor effect. Outcomes after ibrutinib discontinuation are poor.² Early detection of *BTK* and *PLCG2* mutations represents an opportunity for preemptive intervention to eliminate the resistant clone.²
- Duvelisib is a dual PI3K- γ and δ inhibitor. Duvelisib monotherapy improved progression-free survival and overall response rate compared to ofatumumab and had a manageable safety profile in subjects with previously treated CLL/SLL.⁶ Based on these results, duvelisib received US approval for CLL/SLL after at least 2 prior therapies.
- This study will assess duvelisib in patients who develop disease progression or *BTK* and/or *PLCG2* mutations on ibrutinib. Duvelisib will overlap with ibrutinib for the first six 28-day cycles to prevent disease acceleration often seen in patients who discontinue ibrutinib.

Primary Objective:

- To investigate the rate of overall response to duvelisib in patients with ibrutinib-resistant CLL.

Key Eligibility Criteria:

- Patients on current treatment for CLL/SLL with ibrutinib and at least one of the following:
 - *BTK* and/or *PLCG2* mutations
 - Progressive CLL per iwCLL guidelines⁷
- Patients with known Richter transformation will be excluded.

Design:

- This is a single-center, single-arm, open-label phase 2 study with a safety lead-in cohort.
- Treatment plan: Duvelisib will be administered with ibrutinib for the first six 28-day cycles then duvelisib monotherapy will be administered continuously until disease progression or intolerance.

Study Duration: 5 years.

Participant Duration: until disease progression or intolerance.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1.0 OBJECTIVES

1.1 Primary Objective

- To investigate the rate of overall response to duvelisib in patients with ibrutinib-resistant CLL

1.2 Secondary Objectives

- Progression-free survival (time from treatment initiation to progression of disease or death from any cause)
- Overall survival (time from treatment initiation to death from any cause)
- Duration of response (time from initial response to progression of disease)
- Best response
- Safety of duvelisib plus ibrutinib combination
- Safety of duvelisib monotherapy

1.3 Exploratory Objectives

- Immune cell profiling at baseline, during combination treatment with ibrutinib plus duvelisib, and during duvelisib monotherapy
- Minimal residual disease by flow cytometry in peripheral blood and/or bone marrow
- Quantification of allele frequency of *BTK* and *PLCG2* mutations (if present at baseline) during treatment
- Targeted or whole exome sequencing of sequential tumor samples to assess clonal evolution.

2.0 BACKGROUND & RATIONALE

2.1 Chronic Lymphocytic Leukemia and/or Small Lymphocytic Lymphoma

The World Health Organization classification of hematopoietic neoplasias describes CLL as a leukemic, lymphocytic lymphoma, being only distinguishable from SLL by its leukemic appearance.⁸ In the National Cancer Institute (NCI)-Working Group (WG) guidelines, the diagnosis of CLL requires the presence of at least 5×10^9 clonal B lymphocytes/L ($5000/\mu\text{L}$) in the peripheral blood. The definition of SLL requires the presence of lymphadenopathy and/or splenomegaly. Clonal B lymphocytes in the peripheral blood should not exceed $5 \times 10^9/\text{L}$ and the diagnosis should be confirmed by histopathologic evaluation of a lymph node biopsy when possible.⁹

Chronic lymphocytic leukemia/small lymphocytic lymphoma cells co-express the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23. The levels of surface immunoglobulin, CD20, and CD79b are characteristically low compared with those found on normal B cells. Each clone of leukemia cells is restricted to expression of either kappa or lambda immunoglobulin light chains.⁹

For the purposes of this study, the term “CLL” will encompass both CLL and SLL.

2.2 Pathophysiology

CLL is characterized by a progressive accumulation of functionally incompetent lymphocytes. It is believed that antigenic stimulation, along with interactions of accessory cells, cytokines, and tumor microenvironment are promoting factors that stimulate proliferation of CLL cells and allows them to avoid apoptosis. These effects may differ in distinct CLL subgroups and thereby lead to the heterogeneity seen in clinical outcomes among individual cases.

The tumor microenvironment is known to play an important role in the development and maintenance of CLL. Important contributors to this permissive microenvironment include cellular components such as macrophages, T cells, or stromal follicular dendritic cells, and essential proteins (chemokines, cytokines, and angiogenic factors) which exert their oncogenic support via interactions with membrane receptors on the malignant cells. CLL cultured *in vitro* undergo apoptosis, but they can be rescued by coculturing with stromal cells or in presence of soluble factors.¹⁰

In human, T and leukemic B cells aggregate to form ‘proliferation centers’ within bone marrow (BM) and lymphoid tissues, where these rallied cells form immune synapses.¹¹ CD40 ligand form a crosstalk between T and CLL cells which stimulates leukemic B cell survival and promotes resistance to apoptosis.^{12,13} In addition, T cells in CLL are functionally¹¹ and phenotypically¹⁴ defective, and allow malignant B cells to escape immune surveillance. “Pseudo-exhaustion” of effector T cells is explained by increased expression of immune checkpoints on CLL cells^{11,15} and by increased number of regulatory T cells in CLL patients.¹⁶

Myeloid cells, in particular tumor associated macrophages (TAMs) and myeloid derived suppressor cells (MDSCs) are also important in the pathogenesis of CLL.^{17,18} *In vitro*, TAMs support the survival of CLL cells by cell-cell contact and the secretion of immunosuppressive cytokines.^{19,20} MDSCs are immunosuppressive cells that are found at increased frequency in CLL patients compared to healthy individuals and are associated with shorter lymphocyte doubling time.²¹⁻²³ Both TAMs and MDSCs impair tumor immune surveillance via expansion of Treg cells and suppression of T-cell activation in CLL.^{17,21,24}

2.3 Epidemiology and Clinical Course of Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is the most common leukemia of adults in Western countries with an annual incidence of 2 to 4.5 per 100,000 in the general population. According to the NCI Surveillance Epidemiology and End Results (SEER) data, it is estimated that 14,990 men and women (8,870 men and 6,120 women) will be diagnosed with CLL. It affects males twice as frequently as females and is a disease of older individuals (median age 73.0 years for Whites).²⁵ The highest rates of incidence are seen in Caucasians followed by African Americans. Lower rates of incidence are seen in Asian and Hispanic populations.

The complications of CLL usually arise from progressive disease. These complications are, but not limited to infection, hematologic abnormalities, immune phenomena, secondary cancers, and disease transformation. It has been estimated that up to 70% of patients with CLL will develop infections, and infections account for about 55% of deaths in patients with CLL. Hematologic abnormalities include autoimmune hemolytic anemia (AIHA) in approximately 37% of patients, pure red cell aplasia in 6% of patients, and immune mediated thrombocytopenia in 2 to 4% of patients.²⁶ Secondary cancers are noted in about 11% of cases such as acute myeloid leukemia and other solid malignancies. Finally, disease transformation into other forms or more aggressive lymphomas such as diffuse large B-cell lymphoma and Hodgkin’s lymphoma occur in about 5% of cases.²⁷

2.4 Treatment Options for Ibrutinib-Resistant CLL/SLL

Patients who develop CLL progression on ibrutinib often have limited treatment options. Salvage therapies with reported outcomes are described below.

2.4.1 Salvage Chemoimmunotherapy

In a retrospective cohort study of 391 CLL patients treated with frontline ibrutinib, 55 patient were treated with a subsequent therapy after ibrutinib discontinuation.²⁸ Anti-CD20 monoclonal antibody-based chemoimmunotherapy produced an ORR of 50% among 9 patients. However, only 1 had discontinued ibrutinib for CLL progression. Further, a major limitation of conventional chemoimmunotherapy is toxicity. Rates of treatment-related mortality are 3.9% with fludarabine, cyclophosphamide, and rituximab (FCR) and 2.1% with bendamustine and rituximab (BR).²⁹ More than 90% of patients treated with FCR and 78.5% treated with BR experience moderate to severe adverse events equivalent to CTCAE Grade 3 to 5.²⁹ Hematologic toxicities such

as severe neutropenia can occur while on treatment (81.7%) or after treatment completion.³⁰ Infusion reactions related to monoclonal antibodies also limit the successful delivery of treatment. As a part of long-term toxicities, secondary malignancy can occur after being exposed to alkylating agents. Intergroup E2997 trial reported 8.2% cumulative incidence of myeloid neoplasia at 7 years after treatment with fludarabine plus cyclophosphamide (FC).³¹

2.4.2 Stem Cell Transplantation

The EBMT Chronic Malignancies and Lymphoma Working Parties conducted a retrospective study to investigate the safety and efficacy of allogeneic hematopoietic cell transplantation in patients pre-treated with ibrutinib.³² Patients with CLL (n = 48) and mantle cell lymphoma (n = 22) were included in the analysis. In the CLL group, 12-month non-relapse mortality, relapse incidence (RI), progression-free survival (PFS), and overall survival (OS) were 10, 30, 60, and 72%, respectively. Prior ibrutinib failure and poor performance status were risk factors for unfavorable RI, PFS, and OS.

2.4.3 Chimeric Antigen Receptor-Modified T cells

Anti-CD19 chimeric antigen receptor-modified T (CAR-T) cell therapy produced an ORR of 71% among 24 patients with CLL following prior ibrutinib therapy, including 19 who had experienced disease progression while receiving ibrutinib.³³ Undetectable minimal residual disease in the marrow by deep IGH sequencing was achieved in 7 of 12 (58%) who underwent testing. However, the benefit of a deep response should be evaluated against considerable toxicity – 20 patients (83%) developed cytokine release syndrome and 8 patients (33%) developed neurotoxicity with 1 fatal outcome. Interestingly, continuing ibrutinib therapy during CAR-T cell administration appears to reduce cytokine release syndrome while improving efficacy.^{34,35}

2.4.4 Targeted Agents

Idelalisib

Idelalisib selectively inhibits p110 δ isoform of phosphoinositide-3-kinase (PI3K). A phase I study enrolled 54 heavily pretreated relapsed/refractory CLL patients, and demonstrated ORR of 73% with 6 different dose levels of oral idelalisib (range 50-350 mg once or twice daily).³⁶ The highest median PFS was seen in patients receiving 150 mg twice daily or greater (median PFS of 29 months), and no dose-limiting toxicities was observed. Using the 150 mg twice daily dosing, the combination of idelalisib and rituximab was compared to placebo and rituximab in a randomized phase 3 trial.³⁷ The idelalisib arm had a higher ORR (81% vs 13%, p < 0.001) and 12-month OS (92% vs 80%, p = 0.02) compared to the placebo arm. Idelalisib, combined with rituximab, is approved in the U.S. for the treatment of patients with relapsed CLL, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities, and for patients with SLL who have received ≥ 2 prior systemic therapies. In a multicenter, retrospective cohort study, treatment with idelalisib resulted in an overall response rate of 46% among 37 CLL patients after ibrutinib discontinuation for any reason.³⁸ A retrospective study of the French Innovative Leukemia Organization (FILO) reported an ORR of 72% to idelalisib after ibrutinib discontinuation among 29 CLL patients.³⁹

Venetoclax

CLL has dysfunctional intrinsic apoptotic pathways due to the mutation of genes encoding pro-apoptotic proteins, such as p53, or due to overexpression of anti-apoptotic proteins, such as Bcl-2. Venetoclax is a potent, orally bioavailable, small molecule inhibitor of Bcl-2 that induces apoptosis.⁴⁰ A phase I study with venetoclax led to deep and durable remissions in 84 patients with relapsed/refractory CLL (CR or CRi in 22%).⁴¹ The most common adverse events were diarrhea (46%), neutropenia (43%), fatigue (34%), upper respiratory tract infection (29%), and cough (25%). Notably, early studies reported an 11% incidence of grade 3-4 tumor lysis syndrome, which decreased to <5% after dose modification with a ramp-up schedule adopted for later studies. In a randomized, phase 3 trial, 389 patients were randomized to venetoclax plus rituximab or BR. PFS was significantly longer in the venetoclax plus rituximab group than the BR group (median not reached vs 17

months, $p < 0.001$).⁴² With extended follow-up, the venetoclax plus rituximab group also had improved OS (87.9% vs 79.5% at 3 years, $p = 0.0093$).⁴³ Venetoclax is approved as a single agent or in combination with rituximab for treatment of CLL after at least one prior therapy. An interim analysis of 91 patients treated with venetoclax after ibrutinib discontinuation in a multicenter, phase 2 study reported an ORR of 65% (95% CI 53-74), a median PFS of 24.7 months, and an estimated PFS rate at 12 months of 75%.⁴⁴ In exploratory post-hoc subgroup analysis, the ORR was 54% (95% CI 39-68) among patients who discontinued ibrutinib for disease progression compared to 63% (95% CI 44-80) among patients who discontinued ibrutinib for toxicity.

2.5 Duvelisib

2.5.1 Mechanism of Action

Duvelisib is an oral dual inhibitor of PI3K- δ and PI3K- γ , within the pharmacological class of kinase inhibitors and is being developed as a therapeutic in hematologic malignancies. PI3Ks catalyze the production of phosphatidylinositol (3, 4, 5)- trisphosphate (PIP3), leading to activation of downstream effector pathways important for cellular survival, differentiation, and function. There are 4 mammalian isoforms of class 1 PI3Ks: PI3K- α , β , δ (class 1a), and PI3K- γ (class 1b). PI3K- α and PI3K- β are widely expressed and are important mediators of signaling from cell surface receptors. PI3K- α is the isoform most often found mutated in cancers and has a role in insulin signaling and glucose homeostasis.^{45,46} PI3K- β is activated in cancers where phosphatase and tensin homolog (PTEN) is deleted. Both isoforms are targets of small molecule therapeutics in development for cancer. PI3K- δ and PI3K- γ are preferentially expressed in leukocytes and are important in leukocyte function.

The PI3K- δ and PI3K- γ isoforms play essential roles in normal immune cell function and are also expressed in malignant hematopoietic cells. Pathways mediated by PI3K- δ and PI3K- γ are involved in diverse processes of cell growth, survival, proliferation, migration, differentiation, and metabolism. Since central regulatory roles for either or both enzymes have been demonstrated in B cells,⁴⁶⁻⁵⁴ T cells,⁵⁵⁻⁶⁴ neutrophils,⁶⁵ macrophages/monocytes,⁶⁵⁻⁶⁸ mast cells,⁶⁹⁻⁷¹ and natural killer (NK) cells,⁷²⁻⁷⁵ both PI3K- δ and PI3K- γ are believed to be important for the development and persistence of autoimmune disease and hematologic malignancies.

2.5.2 Absorption, Distribution, Metabolism, and Excretion

Duvelisib is rapidly absorbed following oral administration, with maximal concentrations occurring approximately 0.5 to 2 hours after dosing. Exposure (C_{max} and AUC) increased proportionally over a dose range of 1 to 30 mg (single dose) and 1 to 5 mg BID (multiple dose) in healthy subjects. The increase in exposure was slightly less than dose proportional following administration of doses up to 100 mg BID in subjects with hematologic malignancies. In healthy subjects, the absolute oral bioavailability of duvelisib was 42%. In oncology subjects, the mean $t_{1/2}$ of duvelisib ranged from 2.7 to 7.5 hours following multiple dose administration. Based on the $t_{1/2}$, steady state concentrations of duvelisib are expected to be reached within 48 to 72 hours. Accumulation was < 3 -fold with twice daily dosing.

Duvelisib is approximately 99% bound to human plasma proteins at a concentration of 3 μ M (approximate C_{max} following 25 mg BID). The steady-state volume of distribution (V_{ss}) for duvelisib following intravenous (IV) infusion was 12.3 L, suggesting duvelisib distributes into tissues.

In vitro data indicate duvelisib is metabolized primarily by CYP3A4. The primary circulating entity other than parent drug is the inactive, mono-oxidation metabolite, IPI-656. Following single dose administration of duvelisib (25 mg) to healthy male subjects, overall exposure to IPI- 656 relative to duvelisib was approximately 1.4:1. In oncology subjects, steady state exposure to IPI-656 approximated that of the parent drug.

Similar to preclinical species, duvelisib and its metabolites are primarily excreted in feces, with minimal renal elimination of the parent drug in humans. Following oral administration of ¹⁴C-labeled duvelisib to healthy

subjects, 92.5% of the radioactive dose was recovered, with 79.0% and 13.5% recovered in feces and urine, respectively. Less than 1% of the administered dose was excreted in urine as unchanged duvelisib.

2.5.3 Drug-Drug Interactions

In vitro metabolism studies indicate that CYP3A4 is the predominant human CYP isozyme responsible for the metabolism of duvelisib; therefore, exposure to duvelisib could be impacted by other drugs that inhibit or induce CYP3A activity. In Study IPI-145-01, coadministration of ketoconazole (200 mg BID for 5 days) with a single 10 mg dose of duvelisib increased duvelisib C_{max} and AUC(0-inf) by 66% and 295%, respectively, compared to administration of duvelisib alone. PBPK simulations on coadministration of duvelisib 25 mg and 75 mg plus ketoconazole 200 mg BID to steady-state indicated increases in duvelisib exposure of approximately 1.59- and 1.45-fold, respectively. In addition, PBPK simulations demonstrated that the steady-state duvelisib 25 mg BID and 75 mg BID concentration (without ketoconazole) is comparable to steady-state duvelisib 15 mg BID and 40 mg BID concentration (with coadministration of ketoconazole), respectively, in subjects with advanced hematological malignancies.

In Study IPI-145-11, exposure to duvelisib was reduced by approximately 80% when coadministered with rifampin (600 mg daily for 7 days), a strong CYP3A inducer. Based on these data, the concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A is not allowed during treatment with duvelisib.

In vitro studies in human liver microsomes demonstrated that duvelisib and its primary metabolite IPI-656 are reversible inhibitors of CYP2C8 and CYP3A4 and mechanism-based inhibitors of CYP3A4. Model-based methods and PBPK modelling indicated low probability for duvelisib and IPI-656 to cause a clinically meaningful DDI with CYP2C8 substrates but predicted duvelisib and IPI-656 to cause clinically meaningful DDI with CYP3A4 substrates. In Study IPI-145-10, coadministration of duvelisib (25 mg BID for 5 days) with midazolam (MDZ), a sensitive CYP3A substrate, resulted in an approximate 4-fold increase in MDZ systemic exposure (AUC) compared to administration of MDZ alone. PBPK modeling with MDZ predicted that in subjects with advanced hematologic malignancies, duvelisib and IPI-656 concentrations resulting from 25 and 75 mg BID doses would lead to approximately 5.82- and 7.37-fold MDZ exposure increases, respectively.

Metabolism is the main route of elimination for ibrutinib. Ibrutinib is metabolized to several metabolites primarily by CYP3A and to a minor extent by CYP2D6. In vitro studies suggest that ibrutinib and PCI-45227 are unlikely to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A at clinical doses. Both ibrutinib and PCI-45227 are unlikely to induce CYP1A2, CYP2B6 or CYP3A at clinical doses. Therefore, coadministration of duvelisib and ibrutinib may potentially increase systemic exposure to ibrutinib only.

2.5.4 Clinical Experience in CLL

Study IPI-145-07 is a 2-arm, randomized, open-label, Phase 3 study designed to evaluate the efficacy and safety of duvelisib compared with ofatumumab. Eligible subjects were randomized in a 1:1 ratio to 1 of 2 treatment arms: Arm 1 (duvelisib 25 mg BID) or Arm 2 (ofatumumab). Subjects randomized to duvelisib received duvelisib continuously until disease progression, subject withdrawal, or initiation of additional anticancer therapy. Subjects randomized to ofatumumab received ofatumumab per the approved prescribing information. A total of 319 subjects were randomized (duvelisib: 160 subjects; ofatumumab: 159 subjects). Duvelisib monotherapy resulted in statistically significant improvement in PFS and ORR compared to ofatumumab. The median PFS (months from randomization to either progressive disease or death) for duvelisib was 13.3 months (95% CI: 12.1, 16.8) and for ofatumumab was 9.9 months (95% CI: 9.2, 11.3) ($p < 0.0001$).⁶ ORR per modified International Workshop on CLL (IWCLL)/IWG criteria showed statistically significant superiority for duvelisib vs ofatumumab, with an ORR per IRC of 73.8% for duvelisib vs 45.3% for ofatumumab ($p < 0.0001$).⁶ Reductions in target lymph nodes were observed in most subjects treated with duvelisib (85%), representing a statistically significant treatment effect over ofatumumab (16%) ($p < 0.0001$).⁶ Duvelisib is approved in the US for the treatment of relapsed or refractory CLL/SLL after ≥ 2 prior therapies and relapsed or refractory FL after ≥ 2 prior systemic therapies.

The overall hematologic malignancies safety data analyses population is comprised of pooled data as of 19 July 2018 from studies IPI-145-02, IPI-145-06, IPI-145-07, IPI 145-12, and VS-0145-225 (n=588). Adverse events were analyzed for the overall heme safety population and included sub-set analyses for subjects with CLL/SLL or FL. In general, the safety profiles of the three populations were very similar, with the most frequent treatment-emergent adverse events (TEAEs) reported in the overall heme population being diarrhea/colitis (49.0%), neutropenia (34.7%), rash (34.7%), fatigue (33.2%), upper respiratory tract infections (22.3%) and pneumonia (21.6%). Grade 3 or higher TEAEs occurring in $\geq 10\%$ of subjects were: neutropenia (30.1%), diarrhea/colitis (21.6%), pneumonia (16.5%), anemia (12.4%), transaminase elevation (11.4%), thrombocytopenia (11.7%) and rash (10.7%). 226 (38.4%) subjects had an TEAE leading to discontinuation of duvelisib. The most common TEAEs leading to study drug discontinuation ($\geq 2\%$ of subjects) were: diarrhea/colitis (10.0%), rash (3.4%), pneumonia (3.2%), pneumonitis (2.9%), disease progression (2.7%) and transaminase elevation (2.7%). Treatment-emergent serious adverse events (TESAEs) occurred in 400 (68.0%) subjects. The most frequent TESAEs ($\geq 2\%$) were: pneumonia (18.0%), diarrhea/colitis (17.7%), febrile neutropenia (7.0%), disease progression (6.1%), sepsis (5.4%), rash (5.1%), pyrexia (4.9%), pneumonitis (4.4%), renal insufficiency (3.6%), lower respiratory tract infection (3.4%), thrombosis or thromboembolism (2.4%) and upper respiratory tract infection (2.2%). In the All Heme group, 87 (14.8%) subjects experienced a TESAE leading to death. The most frequent fatal TESAEs (>1 subject) were disease progression (35 subjects, 6.0%), pneumonia (15 subjects, 2.6%), sepsis (11 subjects, 1.9%), cardiac failure, respiratory failure (3 subjects each, 0.5% each), and hemorrhage intracranial, multi-organ failure, pneumonitis, rash (2 subjects each, 0.3% each). In CLL/SLL subjects, the most frequent fatal TESAEs were pneumonia (10 subjects, 3.0%), sepsis (9 subjects, 2.7%), disease progression (8 subjects, 2.4%), and cardiac failure, multi-organ failure (2 subjects each, 0.6% each).

2.6 Clinical and Scientific Justification for Protocol Design

In chronic lymphocytic leukemia (CLL), ibrutinib resistance is predominantly caused by somatic mutations in *BTK* (C481) and *PLCG2* (e.g. R665, S707, L846).¹⁻³ Allele frequencies of mutations associated with ibrutinib resistance are often low then increase over time.² Virtually all patients with detectable mutations eventually develop progressive disease.^{2,4} Early detection of *BTK* and *PLCG2* mutations represents an opportunity for preemptive intervention to eliminate the resistant clone.² Outcomes after ibrutinib discontinuation are poor. Survival after disease progression was 3.5 months for Richter transformation and 19.8 months for CLL progression.²

Inhibition of PI3K- δ with idelalisib induces clinical response in a subset of patients previously treated with ibrutinib. In a multicenter, retrospective cohort study, treatment with idelalisib resulted in an overall response rate of 46% among 37 CLL patients after ibrutinib discontinuation for any reason.³⁸ A retrospective study of the French Innovative Leukemia Organization (FILO) reported an ORR of 72% to idelalisib after ibrutinib discontinuation among 29 CLL patients.³⁹

In contrast to idelalisib, duvelisib is a dual inhibitor of PI3K- δ and PI3K- γ . Through inhibition of PI3K- γ , duvelisib inhibits the migration of tumor supportive T cells in response to CXCL12, a chemokine that plays an important role in CLL pathogenesis. Duvelisib also inhibits polarization of macrophages towards the M2 phenotype,⁷⁶ which provide survival signals to CLL cells.^{20,24} In a patient-derived xenograft mouse model, dual inhibition of PI3K- δ and PI3K- γ significantly reduced the number of splenic CLL cells compared to PI3K- δ inhibition alone.⁷⁷ These data suggest that duvelisib may have improved activity in patients with CLL by inhibiting both PI3K- δ and PI3K- γ . In a *BTK*-null X-linked agammaglobulinemia cell line transfected with *BTK* C481S, AKT phosphorylation was abrogated by treatment with duvelisib but not ibrutinib.⁷⁸ Similarly, duvelisib, but not ibrutinib, reduced tumor burden in immunocompromised mice xenografted with peripheral blood mononuclear cells from ibrutinib-resistant patients with *BTK* C481S mutation.⁷⁹

This study investigates duvelisib for patients with CLL who have developed progressive disease or *BTK* and/or *PLCG2* mutations on ibrutinib. In general, and in reported series of patients progressing on ibrutinib, the next

therapy has been administered sequentially. In other words, a drug that has become ineffective is discontinued before a second drug is started. Many clinical studies have required washout periods before the next line of therapy can be started. However, disease acceleration after ibrutinib discontinuation suggests that ibrutinib may still exert at least a partial anti-tumor effect on progressive CLL.⁵ To prevent disease acceleration, this study overlaps duvelisib and ibrutinib for the first six 28-day cycles. The duration of ibrutinib overlap is limited to avoid unnecessary toxicities associated with continuation of a drug (ibrutinib) that has become, at least in part, ineffective at controlling CLL. After the initial period of duvelisib and ibrutinib combination therapy, duvelisib will be continued as a single agent until disease progression or intolerance.

Although the toxicity profiles of duvelisib and ibrutinib as single agents are well recognized, the safety of the combination of duvelisib and ibrutinib has not been evaluated. Duvelisib is associated with immune-related toxicities such as diarrhea/colitis, cutaneous reactions, pneumonitis, transaminase elevation. Several lines of evidence support the hypothesis that coadministration with ibrutinib will improve the tolerability of duvelisib. First, treatment with ibrutinib downregulates inflammatory cytokines in CLL patients⁸⁰ and inhibits cytokine secretion from in vitro activated T cells.⁸¹ Second, continuing ibrutinib therapy during CAR-T cell administration reduced cytokine release syndrome while improving efficacy.^{34,35} Third, ibrutinib is approved for the treatment of graft-versus-host disease after allogeneic transplantation. In a phase 1-1b study combining PI3K δ inhibitor umbralisib with ibrutinib for patients with relapsed or refractory CLL or mantle cell lymphoma, no dose-limiting toxicities (DLTs) were observed and the maximum tolerated dose of umbralisib was not reached.⁸² To evaluate the safety of the combination of duvelisib and ibrutinib, this study will have a safety lead-in cohort starting at duvelisib of 15 mg BID and continuing the subject's dose of ibrutinib at the time of study entry.

2.7 Risk/Benefit Assessment

2.7.1 Identified and Potential Risks Related to Duvelisib

The identified risks for duvelisib treatment are infections, diarrhea/colitis, cutaneous reactions, pneumonitis, transaminase elevation and neutropenia. Potential risks are hepatotoxicity and reproductive toxicity.

Infections

Infection, specifically upper respiratory infection and pneumonia, is one of the most common reported adverse events in subjects who received duvelisib. Serious, including fatal (28/588; 4.8%), infections occurred in 31.6% (186/588) of subjects with hematologic malignancies receiving duvelisib monotherapy. The most common serious infections were pneumonia, sepsis, and lower respiratory infections. In a subset of subjects (n=442, COPIKTRA™ United States Prescribing Information [USPI]), median time to onset of any grade infection was 3 months (range: 1 day to 32 months), with 75% of cases occurring within 6 months. Treat infections prior to initiation of duvelisib. Advise subjects to report any new or worsening signs and symptoms of infection such as fever or chills. For Grade 3 or higher infection, withhold duvelisib until infection has resolved. Resume duvelisib at the same or reduced dose.

Serious, including fatal (3/588; 0.5%), *Pneumocystis jirovecii* pneumonia (PJP) occurred in 1.7% (10/588) of subjects taking duvelisib. Provide prophylaxis for PJP during treatment with duvelisib. Following completion of duvelisib treatment, continue PJP prophylaxis until the absolute CD4+ T cell count is greater than 200 cells/ μ L. Withhold duvelisib in subjects with suspected PJP of any grade, and permanently discontinue if PJP is confirmed. Cytomegalovirus (CMV) reactivation/infection occurred in 1% of subjects taking duvelisib. Consider prophylactic antivirals during duvelisib treatment to prevent CMV infection including CMV reactivation. For clinical CMV infection or viremia, withhold duvelisib until infection or viremia resolves. If duvelisib is resumed, administer the same or reduced dose and monitor subjects for CMV reactivation by PCR or antigen test at least monthly

Diarrhea/Colitis

Serious, including fatal (1/588; 0.2%), diarrhea or colitis occurred in 17.7% (104/588) of subjects with hematologic malignancies receiving duvelisib monotherapy. In a subset of subjects (n=442, COPIKTRA™ USPI), the median time to onset of any grade diarrhea or colitis was 4 months (range: 1 day to 33 months), with 75% of cases occurring by 8 months. The median event duration was 0.5 months (range: 1 day to 29 months; 75th percentile: 1 month). Advise subjects to report any new or worsening diarrhea, stool with mucus or blood, or severe abdominal pain. For non-infectious diarrhea or colitis, follow the guidelines below: For subjects presenting with mild or moderate diarrhea (Grade 1-2) (ie, up to 6 stools per day over baseline) or asymptomatic (Grade 1) colitis, initiate supportive care with antidiarrheal agents as appropriate, continue duvelisib at the current dose, and monitor the subject at least weekly until the event resolves. If the diarrhea is unresponsive to antidiarrheal therapy, withhold duvelisib and initiate supportive therapy with enteric acting steroids (eg, budesonide). Monitor the subject at least weekly. Upon resolution of the diarrhea, consider restarting duvelisib at a reduced dose.

For subjects presenting with abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, or with severe diarrhea (Grade 3) (ie, more than 6 stools per day over baseline) withhold duvelisib and initiate supportive therapy with enteric acting steroids (eg, budesonide) or systemic steroids. A diagnostic work-up to determine etiology, including colonoscopy, should be performed. Monitor at least weekly. Upon resolution of the diarrhea or colitis, restart duvelisib at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue duvelisib. Discontinue duvelisib for life-threatening diarrhea or colitis

Cutaneous Reactions

Serious, including fatal (2/588; 0.3%), cutaneous reactions occurred in 5.1% (30/588) of subjects with hematologic malignancies receiving duvelisib monotherapy. Fatal cases included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN). In a subset of subjects (n=442, COPIKTRA™ USPI), the median time to onset of any grade cutaneous reaction was 3 months (range: 1 day to 29 months, 75th percentile: 6 months), with a median event duration of 1 month (range: 1 day to 37 months, 75th percentile: 2 months). Presenting features for the serious events were primarily described as pruritic, erythematous, or maculo-papular. Less common presenting features include exanthem, desquamation, erythroderma, skin exfoliation, keratinocyte necrosis, and papular rash. Advise subjects to report any new or worsening cutaneous reactions, including painful sores or ulcers on skin, lips, or in the mouth, severe rash with blisters or peeling skin, rash with itching or rash with fever. Review all concomitant medications and discontinue any medications potentially contributing to the event. For subjects presenting with mild or moderate (Grade 1-2) cutaneous reactions, continue duvelisib at the current dose, initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids, and monitor the subject closely. Withhold duvelisib for severe (Grade 3) cutaneous reaction until resolution. Initiate supportive care with steroids (topical or systemic) or anti-histamines (for pruritus). Monitor at least weekly until resolved. Upon resolution of the event, restart duvelisib at a reduced dose. Discontinue duvelisib if severe cutaneous reaction does not improve, worsens, or recurs. For life-threatening cutaneous reactions, discontinue duvelisib. In subjects with Stevens-Johnson syndrome (SJS), TEN, or DRESS of any grade, discontinue duvelisib

Pneumonitis

Serious, including fatal (2/588; 0.3%), pneumonitis without an apparent infectious cause occurred in 4.4% (26/588) of subjects with hematologic malignancies receiving duvelisib monotherapy. In a subset of subjects (n=442, COPIKTRA™ USPI), the median time to onset of any grade pneumonitis was 4 months (range: 9 days to 27 months), with 75% of cases occurring within 9 months). The median event duration was 1 month, with 75% of cases resolving by 2 months.

Advise subjects to report any new or worsening cough or difficulty breathing. Withhold duvelisib in subjects who present with new or progressive pulmonary signs and symptoms such as cough, dyspnea, hypoxia,

interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation and evaluate for etiology. If the pneumonitis is infectious, subjects may be restarted on duvelisib at the previous dose once the infection, pulmonary signs and symptoms resolve. For moderate non-infectious pneumonitis (Grade 2), treat with systemic corticosteroids, and resume duvelisib at a reduced dose upon resolution. If non-infectious pneumonitis recurs or does not respond to steroid therapy, discontinue duvelisib. For severe or life-threatening non-infectious pneumonitis, discontinue duvelisib and treat with systemic steroids.

Transaminase Elevation

TESAEs of ALT and AST elevation occurred in 1.5% (9/588) and 1.4% (8/588) of subjects respectively. TESAE of transaminase increased was reported in 1 subject (0.2%). In a subset of subjects (n=442, COPIKTRA™ USPI), the median time to onset of any grade transaminase elevation was 2 months (range: 3 days to 26 months), with a median event duration of 1 month (range: 1 day to 16 months).

Monitor hepatic function during treatment with duvelisib. For Grade 2 ALT/AST elevation (greater than 3 to 5 × ULN), maintain duvelisib dose and monitor at least weekly until return to less than 3 × ULN. For Grade 3 ALT/AST elevation (greater than 5 to 20 × ULN), withhold duvelisib and monitor at least weekly until return to less than 3 × ULN. Resume duvelisib at the same dose (first occurrence) or at a reduced dose for subsequent occurrence. For Grade 4 ALT/AST elevation (greater than 20 × ULN) discontinue duvelisib.

Neutropenia

Grade 3 or 4 neutropenia occurred in 30.1% (177/588) of subjects with hematologic malignancies receiving duvelisib monotherapy. In a subset of subjects (n=442, COPIKTRA™ USPI), the median time to onset of ≥ Grade 3 neutropenia was 2 months (range: 3 days to 31 months), with 75% of cases occurring within 4 months.

Monitor neutrophil counts at least every 2 weeks for the first 2 months of duvelisib therapy, and at least weekly in subjects with neutrophil counts less than 1.0 Gi/L (Grade 3-4). Withhold duvelisib in subjects presenting with neutrophil counts less than 0.5 Gi/L (Grade 4). Monitor until ANC is greater than 0.5 Gi/L, resume duvelisib at same dose for the first occurrence or a reduced dose for subsequent occurrence. The use of granulocyte-colony stimulating factor (GCSF) when appropriate per ASCO guidelines⁸⁷ is recommended.

Hepatotoxicity

No findings of acute liver failure, or death associated with liver failure, have been observed in any clinical study with duvelisib. However, elevations in ALT and/or AST have been seen in subjects receiving duvelisib. Transaminase elevations were generally asymptomatic and reversible upon stopping drug. Subjects dosed with duvelisib in clinical trials have experienced elevated ALT in combination with elevated bilirubin, typically in the context of a complicated medical history. Elevations generally occurred early in duvelisib dosing, after which duvelisib was held and the events resolved.

Monitor hepatic function during treatment with duvelisib. For Grade 2 ALT/AST elevation (greater than 3 to 5 × ULN), maintain duvelisib dose and monitor at least weekly until return to less than 3 × ULN. For Grade 3 ALT/AST elevation (greater than 5 to 20 × ULN), withhold duvelisib and monitor at least weekly until return to less than 3 × ULN. Resume duvelisib at the same dose (first occurrence) or at a reduced dose for subsequent occurrence. For Grade 4 ALT/AST elevation (greater than 20 × ULN) discontinue duvelisib.

Reproductive Toxicity

There are no available human data informing the associated risk of reproductive toxicity with duvelisib. Pregnant and lactating women are excluded from clinical trials with duvelisib. Based on findings in animals and its mechanism of action, duvelisib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of duvelisib to pregnant rats and rabbits during organogenesis

caused adverse developmental outcomes including embryo-fetal mortality (resorptions, post-implantation loss, and decreased viable fetuses), alterations to growth (lower fetal weights) and structural abnormalities (malformations) at maternal doses approximately 10 times and 39 times the maximum recommended human dose (MRHD) of 25 mg BID in rats and rabbits, respectively. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least 30 days after the last dose.

2.7.2 Identified and Potential Risks Related to Ibrutinib

Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 5.7.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 5.5.1 for guidance on ibrutinib management with surgeries or procedures.

Cardiac Arrhythmias

Atrial fibrillation and atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmia that persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.4.2).

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.4).

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation and pneumocystis pneumonia have occurred in patients treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated

Tumor Lysis Syndrome (TLS)

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of TLS are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

Interstitial lung disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Subjects should be monitored and evaluated for symptoms (eg, dyspnea, cough or pyrexia) and treated symptomatically, including interruption of the suspected agent as appropriate. Should symptoms develop follow the protocol dose modification guidelines.

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes ($>400,000/\mu\text{L}$) may confer increased risk.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., $\geq 50\%$ increase from baseline and an absolute count $>5000/\mu\text{L}$), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/SLL) treated with ibrutinib as a single agent. This effect has also been observed in some subjects with mantle cell lymphoma (MCL) treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL. This pharmacodynamic effect was less prominent or not observed in other indications.

Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

2.7.3 Risks Related to Blood Draws

No major risks are involved with blood draws. Minor complications including bleeding, pain, and hematoma formation at the site of blood draws, vasovagal reactions or infections may rarely occur.

2.7.4 Risks Related to CT Scans

CT (computed tomography) uses special x-ray equipment to obtain image data from different angles around the body and then uses computer processing of the information to show a cross-section of body tissues and organs. Oral and/or intravenous contrast agents will be used and are usually well tolerated. However, some subjects will experience allergic reactions to intravenous contrast. To lower the risk of allergic reactions, low allergenic contrast agents are administered at NIH clinical center. In addition, subjects will be advised that approximately 2-7% of patients who receive contrast agents will experience a temporary reduction in kidney function lasting up to 2 weeks following infusion and that in rare instances, permanent renal damage can result from the use of the IV contrasting agent. Therefore, in subjects with impaired kidney function, we will not use intravenous contrast.

The amount of radiation subjects will receive from the research scans in this study is 1.3 rem of radiation annually, which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. All female subjects will receive pregnancy testing prior to radiation exposure.

2.7.5 Risks Related to Bone Marrow Biopsy

The anesthetic can cause some temporary stinging and burning. A pulling sensation and discomfort may be felt as the marrow is withdrawn. Although rare, there is a potential for bleeding at the site, local infection, and nerve injury causing pain. Bleeding can be stopped by applying local pressure, and infection can be treated with antibiotics.

2.7.6 Risks Related to Lymph Node Biopsy

The anesthetic can cause some temporary stinging and burning. After a core needle biopsy, the site may be tender for 2 to 3 days.

An excisional biopsy may require general anesthesia. For 1 to 2 days after general anesthesia, subjects may feel tired and have a mild sore throat from intubation. After an excisional biopsy, the site may feel tender, firm, swollen, and/or bruised.

2.7.7 Risks Related to Lymphapheresis

The possible risks from lymphapheresis include bleeding from the site where the blood is extracted and returned, lightheadedness, infection, low blood pressure, and muscle cramping.

Known Potential Benefits

Duvelisib is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies. This indication is approved under accelerated approval based on efficacy and safety analysis of patients with at least 2 prior lines of therapy.

Assessment of Potential Risks and Benefits

The median survival after CLL progression on ibrutinib is only 19.8 months.² Treatment options after ibrutinib discontinuation are limited. The potential to achieve remission and prolong survival with duvelisib therapy for these patients outweighs the known potential risks of treatment.

3.0 STUDY DESIGN

This is a single-center, open-label phase 2 study for CLL patients who have developed progressive disease or *BTK* and/or *PLCG2* mutations on ibrutinib. The study has a single treatment arm using duvelisib with ibrutinib for the first six 28-day cycles followed by duvelisib alone. Treatment plan is discussed in detail in Section 6.0.

Notwithstanding the expectation that tolerability of the combination will be favorable, there will be a safety lead-in based on a 3+3 dose-escalation design (Table 1). The starting dose will be duvelisib 15 mg BID and continuing the subject's dose of ibrutinib at the time of study entry. The maximum tolerated dose (MTD) is defined as the highest dose at which 0 or 1 subject out of 6 subjects has experienced a DLT. The decision to escalate, de-escalate or suspend dose escalation is outlined in Table 1. If the MTD is determined to be duvelisib 25 mg BID, subjects enrolled at DL₁ will increase the dose of duvelisib to 25 mg BID after the first cycle or at the time MTD is determined, whichever occurs later. During the safety lead-in, subjects will be enrolled ≥ 1 week apart between each subject. Subjects enrolled in the safety lead-in will be included in the analysis of study endpoints.

Table 1. Dose De-escalation Rules Based on Number of Subjects with DLTs

Number of Patients with DLTs	Decision
DL₁: duvelisib 15 mg BID	
0 DLT out of 3 subjects	Enroll up to 3 subjects at DL ₂
1 DLT out of 3 subjects	Enroll up to 3 more subjects at DL ₁
1 DLT out of 6 subjects	Enroll up to 3 subjects at DL ₂
≥ 2 DLT out of 4 to 6 subjects	Terminate study
DL₂: duvelisib 25 mg BID	
0 DLT out of 3 subjects	Proceed to phase 2 study at DL ₂
1 DLT out of 3 subjects	Enroll up to 3 additional subjects at DL ₂
1 DLT out of 6 subjects	Proceed to phase 2 study at DL ₂
≥ 2 DLT out of 4 to 6 subjects	Enroll up to 3 additional subjects at DL ₁ if only 3 subjects have been treated at DL ₁ . Enroll up to 33 subjects at DL ₁ if 0-1 DLT found in the first 6 subjects treated.

The study will use a Simon two-stage minimax design and enroll 18 subjects in the first stage. If ≤ 4 subjects achieve a response, the study will stop for futility; otherwise, the study will proceed to the second stage and enroll an additional 15 subjects for a total of 33 evaluable subjects.

4.0 ELIGIBILITY ASSESSMENT AND ENROLLMENT

4.1 Inclusion Criteria

- Age ≥ 18 years
- Diagnosis of CLL or SLL as defined by the following:
 - CLL: clonal B cells $\geq 5,000$ cells/ μ L in the peripheral blood.
 - SLL: lymphadenopathy with histopathological evaluation consistent with SLL, absence of cytopenia caused by clonal marrow infiltrate, and $<5,000$ B cells/ μ L in the peripheral blood

- Immunophenotype: co-expression of CD5, CD19, CD20, and CD23. CD23 negative cases may be included if there is an absence of t(11;14).
 - Current treatment with ibrutinib for CLL.
 - Mutations in *BTK* and/or *PLCG2* (from a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory) with measurable disease characterized by at least 1 of the following:
 - Lymphadenopathy: ≥ 1 lymph node measuring ≥ 1.5 cm in the greatest diameter
 - Splenomegaly: spleen measuring > 13 cm in craniocaudal length
 - Lymphocytosis: $\geq 5,000$ B cells/ μL
 - Bone marrow infiltration: CLL comprising $\geq 30\%$ of all cells
- or
- Progressive disease characterized by at least 1 of the following when compared with nadir values:
- Lymphadenopathy: appearance of any new enlarged lymph nodes (≥ 1.5 cm) or an increase by $\geq 50\%$ in greatest determined diameter of any previous site (≥ 1.5 cm).
 - Splenomegaly: an increase in the cranio-caudal dimension of the spleen by ≥ 2 cm from nadir, on imaging or physical exam.
 - Lymphocytosis: an increase in the number of blood lymphocytes by $\geq 50\%$ over nadir with $\geq 5,000$ cells/ μL B cells not attributable to redistribution of leukemia cells from lymphoid tissues to the blood related to treatment with kinase inhibitor.
 - Cytopenia: occurrence of cytopenia directly attributable to CLL and unrelated to autoimmune cytopenia or treatment, as documented by a decrease of Hb levels ≥ 2 g/dL or < 10 g/dL, or by a decrease of platelet counts $\geq 50\%$ or $< 100,000/\mu\text{L}$, if the marrow biopsy is consistent with the cytopenia resulting from increased marrow infiltration of clonal CLL cells.
 - Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 .
 - Adequate organ function as defined in Table 2.

Table 2. Summary of adequate organ function for eligibility

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1000/\mu\text{L}$
Platelets	$\geq 75,000/\mu\text{L}$
Renal	
Serum creatinine	< 2.0 mg/dL
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN except subjects with Gilbert's Syndrome
AST (SGOT) and ALT (SGPT)	≤ 3.0 X ULN

- For women of childbearing potential (WCBP): negative serum β human chorionic gonadotropin (βhCG) pregnancy test within 7 days before first treatment (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months for women > 55 years of age)
- Willingness of male and female subjects who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control for the duration of the study treatment and 3 months after the last dose of duvelisib
- Willingness and ability to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty
- Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

4.2 Exclusion Criteria

- Richter transformation of CLL into an aggressive lymphoma

- History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function
- Prior history of drug-induced colitis or pneumonitis
- Known hypersensitivity to any of the study drugs
- Major surgery within 4 weeks prior to screening
- Central nervous system (CNS) non-Hodgkin lymphoma (NHL); lumbar puncture not required unless CNS involvement is clinically suspected
- Active cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection (i.e., subjects with detectable viral load)
- Infection with hepatitis B or hepatitis C :
 - Subjects with a positive hepatitis B surface antigen (HBsAg)) will be excluded
 - Subjects with or hepatitis C antibody (HCV Ab) will be excluded, unless they have received curative treatment for hepatitis C virus (HCV) and have undetectable viral RNA by PCR.
 - Subjects with a positive hepatitis B core antibody (HBcAb) must have negative hepatitis B virus (HBV) deoxyribonucleic acid (DNA) to be eligible, must receive prophylaxis with entecavir (or equivalent) concomitant with duvelisib treatment, and must be periodically monitored for HBV reactivation by institutional guidelines
 - Investigators who strongly believe that a positive HBcAb is false due to passive immunization from previous immunoglobulin infusion therapy should consider the risk-benefit for the patient given the potential for reactivation
- Infection with human immunodeficiency virus (HIV):
 - Subjects must be receiving antiretroviral therapy, have undetectable HIV RNA viral load and CD4 cell count $\geq 200/\mu\text{L}$ to be eligible, must continue antiretroviral therapy concomitant with duvelisib treatment, and must be periodically monitored for suppression of viral load and potential drug-drug interactions between antiretroviral therapy and duvelisib
- Infection with human T-lymphotropic virus type 1
- History of tuberculosis treatment within the 2 years prior to randomization
- History of chronic liver disease, veno-occlusive disease, alcohol abuse, or illicit drug use
- Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids >20 mg of prednisone (or equivalent) once daily (QD)
- Ongoing treatment for systemic bacterial, fungal, or viral infection at screening
 - NOTE: Subjects on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met
- Administration of a live or live attenuated vaccine within 6 weeks of randomization
- Concurrent administration of medications or foods that are strong inhibitors or inducers of cytochrome P450 3A (CYP3A). No prior use within 2 weeks before the start of study intervention.
- Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster (VZV) at screening
- Baseline left ventricular ejection fraction (LVEF) $< 45\%$
- Baseline QT interval corrected with Fridericia's method (QTcF) > 500 ms
 - NOTE: criterion does not apply to subjects with a right or left bundle branch block (BBB)
- Subjects with clinically significant medical condition of malabsorption, inflammatory bowel disease, chronic conditions which manifest with diarrhea, refractory nausea, vomiting, or any other condition that will interfere significantly with drug absorption
- Female subjects who are pregnant or breastfeeding
- Concurrent active malignancy that requires treatment except malignancies treated with antihormonal therapy alone, nonmelanoma skin cancer, or carcinoma in situ of the cervix.
- History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or a pacemaker within the last 6 months prior to screening
- Unstable or severe uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition, uncontrolled diabetes and inflammatory GI diseases such as Crohn's Disease) or any important

medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the risk to the subject associated with his or her participation in the study

5.0 TREATMENT PLAN

5.1 Drug Administration

Duvelisib is an orally administered product. Duvelisib will be administered with or without food. The drug dose is 25 mg BID or 15 mg BID. The capsules should be swallowed whole. Each dose of duvelisib is taken around the same time each day. If a dose is missed by fewer than 6 hours, subjects will take the missed dose immediately and take the next dose as usual. If a dose is missed by more than 6 hours, subjects will wait and take the next dose at the usual time.

Ibrutinib is an orally administered product. Ibrutinib will be administered with a glass of water and with or without food. Subjects will continue the same dose of ibrutinib prior to study enrollment for the first six 28-day cycles. Each dose of ibrutinib is taken around the same time each day. The capsules should not be opened, broken, or chewed. The tablets should not be cut, crushed, or chewed.

5.2 Treatment Schedule

All cycles will be 28 (\pm 7) days long. In cycles 1-6, duvelisib and ibrutinib will be administered. From cycle 7 onwards, duvelisib will be administered alone until disease progression or intolerance.

5.3 Dose Limiting Toxicities

The DLT evaluation period is defined as the first cycle after starting duvelisib. The following will qualify for a DLT:

- Death related to duvelisib or ibrutinib
- Any AE which leads to discontinuation or decrease in duvelisib dose per Sections 5.4.1 and 5.5.1 during the DLT window

5.4 Dose Modification Guidelines

5.4.1 Dose Modification of Duvelisib

Toxicities attributed to duvelisib will be managed per Table 3, Table 4 and Section 11.2.1 with dose reduction, treatment hold, or discontinuation of duvelisib.

Table 3. Duvelisib Dose Modification and Toxicity Management

Toxicity	Grade	Management
Non-hematologic		
Infections	Grade \geq 3	<ul style="list-style-type: none">• Withhold duvelisib until resolved• Duvelisib can be resumed at the same or reduced dose after resolution of a grade \geq 3 infection based on the discretion of the Investigator (Table 4)
	Clinical CMV infection or viremia (positive PCR or antigen test)	<ul style="list-style-type: none">• Withhold duvelisib until resolved• Resume at the same or reduced dose (Table 4)• If duvelisib is resumed, monitor patients for CMV reactivation (by PCR or antigen test) at least monthly
	PJP	<ul style="list-style-type: none">• For suspected PJP, withhold duvelisib until evaluated• For confirmed PJP, discontinue duvelisib
Non-infectious diarrhea or colitis	Mild/moderate diarrhea (Grade 1-2, up to 6	<ul style="list-style-type: none">• No change in dose

	stools per day over baseline) responsive to antidiarrheal agents OR Asymptomatic (Grade 1) colitis	<ul style="list-style-type: none"> Initiate supportive therapy with antidiarrheal agents as appropriate Monitor at least weekly until resolved
	Mild/moderate diarrhea (Grade 1-2, up to 6 stools per day over baseline) unresponsive to antidiarrheal agents	<ul style="list-style-type: none"> Withhold duvelisib until resolved Initiate supportive therapy with enteric acting steroids (e.g., budesonide) Monitor at least weekly until resolved Resume at a reduced dose (see Table 4)
	Severe diarrhea (Grade 3, > 6 stools per day over baseline) OR Abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs	<ul style="list-style-type: none"> Withhold duvelisib until resolved Initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids Monitor at least weekly until resolved Resume at a reduced dose (see Table 4) For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue duvelisib
	Life-threatening	<ul style="list-style-type: none"> Discontinue duvelisib
Cutaneous reactions	Grade 1-2	<ul style="list-style-type: none"> No change in dose Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids Monitor closely
	Grade 3	<ul style="list-style-type: none"> Withhold duvelisib until resolved Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids Monitor at least weekly until resolved Resume at reduced dose (see Table 4) If severe cutaneous reaction does not improve, worsens, or recurs, discontinue duvelisib
	Life-threatening	<ul style="list-style-type: none"> Discontinue duvelisib
	SJS, TEN, DRESS (any grade)	<ul style="list-style-type: none"> Discontinue duvelisib
Pneumonitis without suspected infectious cause	Moderate symptomatic (Grade 2)	<ul style="list-style-type: none"> Withhold duvelisib Treat with systemic steroid therapy If pneumonitis recovers to Grade 0 or 1, duvelisib may be resumed at reduced dose (see Table 4) If non-infectious pneumonitis recurs or patient does not respond to steroid therapy, discontinue duvelisib
	Severe (Grade 3) or life-threatening	<ul style="list-style-type: none"> Discontinue duvelisib Treat with systemic steroid therapy
ALT/AST elevation	3 to 5 × upper limit of normal (ULN) (Grade 2)	<ul style="list-style-type: none"> Maintain duvelisib dose Monitor at least weekly until return to < 3 × ULN
	> 5 to 20 × ULN (Grade 3)	<ul style="list-style-type: none"> Withhold duvelisib and monitor at least weekly until return to < 3 × ULN Resume duvelisib at same dose (first occurrence) or at a reduced dose for subsequent occurrence (see Table 4)
	> 20 × ULN (Grade 4)	<ul style="list-style-type: none"> Discontinue duvelisib
Hematologic		

Neutropenia	Absolute neutrophil count (ANC) 0.5 to 1.0 Gi/L	<ul style="list-style-type: none"> • Maintain duvelisib dose • Monitor ANC at least weekly • G-CSF may be administered per Section 5.5.1
	ANC < 0.5 Gi/L	<ul style="list-style-type: none"> • Withhold duvelisib • Monitor ANC until > 0.5 Gi/L • Resume duvelisib at same dose (first occurrence) or at a reduced dose for subsequent occurrence (see Table 4) • G-CSF may be administered per Section 5.5.1
Thrombocytopenia	Platelet count 25 to < 50 Gi/L (Grade 3) with grade 1 bleeding	<ul style="list-style-type: none"> • No change in dose • Monitor platelet counts at least weekly
	Platelet count 25 to < 50 Gi/L (Grade 3) with grade 2 bleeding OR Platelet count < 25 Gi/L (Grade 4)	<ul style="list-style-type: none"> • Withhold duvelisib • Monitor platelet counts until ≥ 25 Gi/L and resolution of bleeding (if applicable) • Resume duvelisib at same dose (first occurrence) or resume at a reduced dose for subsequent occurrence (see Table 4)

Table 4. Dose Modification Levels

Dose Level	Dose
Initial dose	25 mg BID
Dose reduction	15 mg BID
Subsequent dose reduction	Discontinue duvelisib if subject is unable to tolerate 15 mg BID

5.4.2 Dose Modification of Ibrutinib

Since subjects are on ibrutinib therapy prior to the initiation of duvelisib, treatment-emergent hematologic toxicities will be attributed to duvelisib and managed per Section 5.4.1. Interrupt ibrutinib for any grade ≥ 3 non-hematologic toxicities attributed to ibrutinib. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib may be reinitiated at the original dose. If the toxicity reoccurs, reduce dose by 140 mg per day. A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib.

Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.5 Permanent Discontinuation of Study Drug Administration

Duvelisib and/or ibrutinib may be continued in subjects who develop progressive disease until the start of next treatment for CLL to prevent acceleration of disease related to treatment withholding. Subjects who permanently discontinue study drug administration for treatment-related adverse events will be followed for resolution of the event. Subjects will remain on study until they meet off study criteria in Section 9.7.

5.5.1 Permanent Discontinuation of Duvelisib

- Confirmed PJP
- Life-threatening non-infectious diarrhea or recurrent grade 3 diarrhea
- Life-threatening colitis or recurrent colitis of any grade
- Life-threatening cutaneous reaction or SJS, TENS, or DRESS (any grade) or grade 3 cutaneous reaction that does not improve, worsens, or recurs
- Grade ≥ 3 pneumonitis without suspected infectious cause or grade 2 non-infectious pneumonitis that recurs or does not respond to steroid therapy

- Grade 4 ALT/AST elevation
- Pregnancy or unwillingness to use acceptable method of contraception
- Progressive disease (duvelisib may be continued until the start of next treatment as described above)

5.5.2 Permanent Discontinuation of Ibrutinib

- Life-threatening cardiac arrhythmia
- Pregnancy or unwillingness to use acceptable method of contraception
- Progressive disease (ibrutinib may be continued until the start of next treatment as described above)

5.6 Concomitant Medications and Therapies

Subjects may continue most medications they were prescribed prior to study enrollment for comorbid conditions. All concomitant medications, including over the counter drugs, will be recorded.

5.6.1 Supportive Medications and Care

Subjects should receive appropriate supportive care as deemed clinically indicated by the investigator including, but not limited to:

- Pneumocystis jirovecii pneumonia (PJP) prophylaxis: sulfamethoxazole/trimethoprim (or alternative agent in case of sulfa allergy) will be administered during treatment with duvelisib and continued until the absolute CD4+ T-cell count > 200/ μ L
- Antiviral prophylaxis: acyclovir or valacyclovir will be administered during treatment with duvelisib
- Transfusions: packed red blood cells and/or platelets will be transfused as clinically indicated.
- Granulocyte-colony stimulating factor (G-CSF): filgrastim or peg-filgrastim may be administered per American Society of Oncology guidelines.⁸³
- Steroids (e.g. systemic, enteric, or topical) may be administered to manage toxicities.

Refer to Table 3 for duvelisib dose modification and toxicity management.

5.6.2 Medications that Inhibit or Induce CYP3A

CYP3A4 has been identified as the primary contributor to the metabolism of duvelisib and ibrutinib. The concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A (Appendix B) should be avoided during treatment with duvelisib monotherapy or in combination with ibrutinib. Co-administration with a strong CYP3A inhibitor may increase the risk of duvelisib and ibrutinib toxicities. Reduce or withhold the dose of duvelisib and ibrutinib when co-administered with a strong CYP3A4 inhibitor.

5.6.3 QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution during treatment with ibrutinib; periodic ECG and electrolyte monitoring should be considered.

5.6.4 Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Subjects with congenital bleeding diathesis have not been studied. Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g. atrial fibrillation) should be observed closely for signs and symptoms of bleeding and the risks and benefits of continuing ibrutinib treatment should be considered.

5.6.5 Lifestyle Considerations

Birth control

Female subjects of reproductive potential and male subjects with female partners of reproductive potential must use effective contraception during treatment and for at least 30 days after the last dose of duvelisib. Male subjects must also refrain from donating sperm during their participation in the study and for 30 days after the last dose of duvelisib.

Effective methods of contraception include:

- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not effective methods of contraception.
- Sterilization
 - Female subject or female partner of male subject: When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
 - Male subject or male partner of female subject: (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Hormonal methods of contraception associated with inhibition of ovulation: oral, implantable, injectable, intravaginal, or transdermal contraception.

Acceptable methods of contraception include:

- Barrier methods of contraception: condom, diaphragm, or cervical/vault cap with spermicidal foam/gel/film/cream/vaginal suppository.

Supplements

Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib.

5.6.6 Prohibited Concomitant Medications and Therapy

Table 5. Duvelisib Prohibited Concomitant Therapies

Prohibited Concomitant Therapy	Guidance
Use of Vaccines	<p>For all subjects, the use of live or live attenuated vaccines is prohibited during the treatment with study intervention.</p> <p>The use of inactivated (or killed) vaccines (such as pneumococcal pneumonia vaccine) is allowed during the study, however subjects and their physicians should be aware that the effectiveness of any vaccine administered concomitantly with duvelisib may be diminished. The ability to generate an immune response to any vaccine following the administration of duvelisib has not been studied.</p>

Prohibited Concomitant Therapy	Guidance
Immunosuppressants	<p>Subjects are not to receive ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids for > 1 week at doses > the equivalent of 20 mg prednisone QD.</p> <p>Note: Acute treatment for underlying autoimmune disorders (e.g., reactive airway disease, rheumatoid arthritis, etc.) with corticosteroid doses > 20 mg prednisone or equivalent QD for ≤ 1 week is permitted during the study. Corticosteroid doses of ≤ 20 mg prednisone or equivalent QD are permitted during the study for physiological replacement or chronic treatment for underlying autoimmune disorders (e.g., reactive airway disease, rheumatoid arthritis, etc.).</p>
Other Anticancer Therapy or Investigational Agents	During study intervention period, subjects are not to receive any additional anticancer therapy or other investigational agents not outlined in the protocol.
Medications or Foods that Strongly Inhibit or Induce CYP3A4	<p>Use of a strong CYP3A inhibitor or inducer is prohibited. Co-administration with a strong CYP3A inhibitor increases duvelisib exposure which may increase the risk of duvelisib toxicities. Co-administration with a strong CYP3A inducer decreases duvelisib exposure which may reduce duvelisib efficacy.</p> <p>Appendix B provides a list of medications and foods known to inhibit (Table 7) or induce (Table 8) CYP3A. Please note that these tables do not provide a comprehensive list of all medications which may modulate CYP3A activity.</p>

Abbreviations: CYP3A: cytochrome P450 3A; QD: once daily

Table 6. Duvelisib Concomitant Therapies: Use with Caution

Concomitant Therapy: Use with Caution	Guidance
Medications or Foods that Weakly or Moderately Inhibit or Induce CYP3A4	<p>Please discuss use of weak or moderate CYP3A inhibitors and inducers with the Medical Monitor.</p> <p>Section XX provides a list of medications and foods known to inhibit (Table XX) or induce (Table XX) CYP3A. Please note that these tables do not provide a comprehensive list of all medications which may modulate CYP3A activity.</p>
Medications that are Substrates of CYP3A	<ul style="list-style-type: none"> Co-administration with duvelisib decreases AUC of a sensitive CYP3A4 substrate which may decrease the efficacy of these drugs. Consider finding an alternative drug that is not a substrate of CYP3A4. Table 9 in Appendix B provides a list of medications known to be substrates of CYP3A. Please note that Table XX <p>Table is not a comprehensive list of all medications which may be substrates of CYP3A. The Sponsor should be contacted with any questions regarding concomitant use of medications that are CYP3A substrates.</p>

Abbreviations: AUC: area under the curve; CYP3A: cytochrome P450 3A; QD: once daily.

6.0 CLINICAL EVALUATIONS

Procedures or tests conducted at outside institutions or as part of other NIH protocols may be used for screening or baseline purposes provided they were performed within the defined time frame.

6.1 Screening and Baseline Assessments

Screening assessment for subject eligibility will be performed as part of 97-H-0041 or other NIH protocols. Subject eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria as detailed in Section 4.0. Baseline tests will be performed within 4 weeks before starting duvelisib, unless otherwise specified.

- AE/SAE assessment: the AE reporting period begins from the time that the patient provides informed consent through and including 30 calendar days after the last study drug dose.
- Medical history: clinically relevant past medical history includes medical diagnoses and/or conditions that are 1) currently ongoing, or 2) occurred within 1 year of study enrollment, or 3) occurred before 1 year of study enrollment and potentially associated with major organ dysfunction or long-term sequelae (e.g. hypertension, hyperlipidemia, diabetes, surgery of major organ system, any malignancy except non-melanoma skin cancer)
- Concomitant medication review
- ECOG performance status (PS)
- Physical exam
- HLA typing (at any time before starting duvelisib)
- Complete blood count (CBC) with differential
- Acute care and mineral panels (includes Na, K, Cl, CO₂, creatinine, glucose, BUN, phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and LDH
- Hepatic panel (includes alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Reticulocyte count
- PT, PTT
- Serum protein electrophoresis with immunofixation (SPEP)
- Serum free light chains and quantitative immunoglobulins
- C-reactive protein (CRP)
- Beta-2 microglobulin (B2M)
- Haptoglobin and direct antiglobulin test (DAT)
- Iron panel (includes ferritin, transferrin, iron), folate, and vitamin B12
- Thyroid function panel (thyroid stimulating hormone, free T4, T3)
- Hepatitis B and C virus Ab (within 12 weeks before starting duvelisib). For subjects with a positive HBcAb, hepatitis B DNA PCR will be performed.
- HIV and HTLV-I/II Ab (within 12 weeks before starting duvelisib)
- CMV and EBV PCR (blood) (within 12 weeks before starting duvelisib)
- Lymphocyte phenotyping (T, B, NK)
- For WCBP, one negative pregnancy tests (within 1 week before starting duvelisib)
- Peripheral blood flow cytometry for CLL
- CLL FISH (includes probes for 11q-, +12, 13q-, 17p-, t(11:14))
- Unstimulated and CpG-stimulated karyotype
- IGHV mutation analysis (at any time before starting duvelisib)
- CT of the neck, chest, abdomen and pelvis
- BM aspirate and biopsy
- EKG
- Research blood (up to 80 mL)
- Lymphapheresis for research (optional)
- Lymph node biopsy for research (optional)

6.2 On Therapy Assessments

6.2.1 Cycles 1-6

Tests will be performed at the end of Cycles 1-6, unless otherwise specified. Each cycle is 28 (\pm 7) days.

- AE/SAE assessment
- Interval history
- Concomitant medication review
- ECOG PS
- Physical exam
- CBC with differential (every 2 weeks for Cycles 1-2, tests conducted at outside institutions are accepted)
- Acute care and mineral panels
- Total protein, uric acid, and LDH
- Hepatic panel
- Reticulocyte count
- CRP
- B2M
- Haptoglobin, DAT
- HBV DNA Quantitative PCR (subjects with positive HBcAb only)

Additional tests will be performed at the end of Cycles 3 and 6.

- Serum free light chains and quantitative immunoglobulins
- Lymphocyte phenotyping (T, B, NK)
- Peripheral blood flow cytometry for CLL (at the end of Cycle 6 only)
- CT of the neck, chest, abdomen and pelvis
- Bone marrow biopsy and aspirate
- Research blood (up to 80 mL)

6.2.2 Cycle 7 Onwards

After Cycle 6, tests will be performed every 3 months (\pm 15 days), unless otherwise specified.

- AE/SAE assessment
- Interval history
- Concomitant medication review
- ECOG PS
- Physical exam
- CBC with differential
- Acute care and mineral panels
- Total protein, uric acid, and LDH
- Hepatic panel
- Reticulocyte count
- B2M
- Haptoglobin, DAT
- HBV DNA Quantitative PCR (subjects with positive HBcAb only)
- Lymphocyte phenotyping (T, B, NK) (every 6 months)
- Peripheral blood flow cytometry for CLL (when subject meets all other criteria for complete remission as detailed in Section 7.0)
- CT of the neck, chest, abdomen and pelvis (after 12 months on duvelisib, then annually)
- Bone marrow biopsy and aspirate (when subject meets all other criteria for complete remission as detailed in Section 7.0)

- Bone marrow flow cytometry for CLL (when subject meets all other criteria for complete remission as detailed in Section 7.0)
- Research blood (up to 80 mL, optional)

6.2.3 Time of Progressive Disease or Suspicion of Progressive Disease

- AE/SAE assessment
- Interval history
- Concomitant medication review
- ECOG PS
- Physical exam
- CBC with differential
- Acute care and mineral panels
- Total protein, uric acid, and LDH
- Hepatic panel
- Reticulocyte count
- B2M
- Haptoglobin, DAT
- Serum free light chains and quantitative immunoglobulins
- CRP
- CMV and EBV PCR (blood)
- Lymphocyte phenotyping (T, B, NK)
- Peripheral blood flow cytometry for CLL
- CT of the neck, chest, abdomen and pelvis
- Research blood (up to 80 mL)
- CLL FISH (includes probes for 11q-, +12, 13q-, 17p-, t(11:14)) (optional)
- Unstimulated and CpG-stimulated karyotype (optional)
- PET scan (optional)
- Bone marrow biopsy and aspirate (optional)
- Bone marrow flow cytometry for CLL (optional)
- Lymph node biopsy (optional)

6.3 Safety Assessment after Permanent Discontinuation of Duvelisib

Safety assessments will be performed in subjects who are able to return for follow-up after permanent discontinuation of duvelisib. Tests will be performed 30 days (+ 7 days) after last dose of duvelisib is administered or before the next treatment starts, whichever occurs first.

- AE/SAE assessment
- Interval history
- Concomitant medication review
- ECOG PS
- Physical exam
- CBC with differential
- Acute care and mineral panels
- Total protein, uric acid, and LDH
- Hepatic panel
- Reticulocyte count
- B2M
- Haptoglobin, DAT
- HBV DNA Quantitative PCR (subjects with positive HBcAb only)
- Lymphocyte phenotyping (T, B, NK)

6.4 Follow-Up Assessments

After the Safety Assessment in Section 6.3, subjects who discontinue treatment for an AE in the absence of disease progression or new anti-CLL therapy will be followed for progression and survival every 6 months (\pm 30 days). After subjects progress or start new anti-CLL therapy, they will be followed yearly (\pm 30 days) for survival. Survival follow-up may be conducted by phone.

Subjects who discontinue treatment for disease progression or start new anti-CLL therapy will be followed yearly (\pm 30 days) for survival. Survival follow-up may be conducted by phone.

7.0 CRITERIA FOR RESPONSE

Response assessments will follow iwCLL 2008 guidelines⁹ and incorporate clarifications for lymphocytosis associated with kinase inhibitors.⁸⁴ Response includes complete response, partial response, and partial response with lymphocytosis (Table 4).

Table 4. Response Definition

Response	CR ^D	PR ^E	PRL	PD ^F	SD ^G
Group A					
Lymph nodes ^A	None \geq 1.5 cm	Decrease \geq 50%	Decrease \geq 50%	Increase \geq 50% or any new lesion $>$ 1.5 cm	Change of -49% to +49%
Spleen and/or liver size ^B	Spleen $<$ 13 cm; liver size normal	Decrease \geq 50%	Decrease \geq 50%	Increase \geq 50% or new splenomegaly	Change of -49% to +49%
Blood lymphocytes	$<$ 4000/ μ L	Decrease \geq 50%	Increase or decrease $<$ 50%	Increase \geq 50% and $>$ 5000/ μ L B cells	Change of -49% to +49%
Group B					
Platelet count	\geq 100, 000/ μ L	\geq 100,000/ μ L or increase \geq 50% over baseline	\geq 100,000/ μ L or increase \geq 50% over baseline	Decrease \geq 50% secondary to CLL	Change of -49% to +49%
Hemoglobin	\geq 11.0 g/dL	\geq 11.0 g/dL or increase \geq 50% over baseline	\geq 11.0 g/dL or increase \geq 50% over baseline	Decrease \geq 50% secondary to CLL	Increase $<$ 11.0 g/dL or $<$ 50% over baseline, or decrease $<$ 2 g/dL
Neutrophils	\geq 1500/ μ L	N/A	N/A	$<$ 1500/ μ L secondary to CLL	N/A
Bone marrow ^C	Normocellular, $<$ 30% lymphocytes, no B-lymphoid nodules	N/A	N/A	N/A	N/A

^A Sum of the products (SPDs) of up to 6 lymph nodes as evaluated by CT scans or if CT scan is unavailable, by physical exam. For PD, at least one of the target lesions should be pathologically enlarged (long axis $>$ 1.5 cm).

^B Spleen and liver size will be assessed by CT scans. Given the impact of numerous medical conditions, liver size should only be counted if hepatomegaly is clearly attributable to lymphoid involvement.

^C Complete response requires confirmation with bone marrow biopsy.

^D For CR, all group A and B parameters must be met. For CR with incomplete marrow recovery (CRi), all criteria must be met, except for persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to CLL, but related to drug toxicity.

^E For PR, at least 2 group A parameters and 1 group B parameter must be met, if previously abnormal. If only 1 parameter of both groups A and B was abnormal before therapy, only 1 needs to improve.

^F For progressive disease (PD), at least 1 parameter must be met on two consecutive assessments within 3 months or transformation to a more aggressive histology. Change in each parameter is relative to baseline or nadir values.

^G For SD, criteria for CR, PR, PRL, or PD have not been met.

Abbreviations

CR: complete remission; CRi: complete response with incomplete marrow recovery; PR: partial remission; PRL: partial remission with lymphocytosis; PD: progressive disease; SD: stable disease

8.0 ANCILLARY LABORATORY RESEARCH STUDIES

8.1 Collection of Samples

Blood samples: A volume not to exceed 550 mL of peripheral blood will be requested during the initial 8-week period. Subsequent research blood draws will typically consist of <100 mL of peripheral blood at follow up visits (not to exceed 550 mL in any 8-week period).

Lymphapheresis: Lymphapheresis procedure for research may be obtained before starting duvelisib, and/or in subjects with persistent lymphocytosis, and/or at progression of disease or suspicion of progressive disease.

Bone marrow biopsies and aspirate: Bone marrow biopsy cylinder and up to 10 mL of bone marrow aspirate may be obtained for research as indicated in Section 6.0.

Lymph node biopsies: An excisional or core needle lymph node biopsies may be obtained before starting duvelisib, and/or during treatment, and/or at progression of disease or suspicion of progressive disease.

During the course of participating on this study, an additional 10 mL of blood (NIH visits only) and 5 mL of bone marrow aspirate each time a patient has a bone marrow examination may be requested. These samples will be stored with the subject's permission for other exploratory laboratory research studies reviewed and approved by the IRB. Research samples will be coded and stored in the secure laboratory of Dr. Wiestner.

8.2 Intended Use

These specimens will not be used for diagnostic purposes.

The translational and correlative endpoints of the study require analysis of samples from blood, bone marrow, and lymph node for immune cell phenotyping and targeted or whole exome sequencing.

Leftover and additional samples may be used for the descriptive or exploratory ancillary research studies, including, but not limited to, studies approved by the NIH Intramural IRB.

8.3 Storage, Tracking and Disposition of Samples and Data

Storage: All samples will be stored in the laboratory of Dr. Wiestner. Collected samples will be de-identified prior to storage following current NHLBI DIR BSI Policy. Efforts to ensure protection of patient information include:

- Each sample is assigned a unique number.

- Vials holding patient samples are labeled with the sequential laboratory accession ID number that does not contain any personal identifier information.
- An electronic database is used to store patient information related to the coded samples
- The laboratory is located in a controlled access building and laboratory doors are kept locked. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.

Tracking: Samples will be ordered and tracked through the CRIS Sunrise. If CRIS Sunrise is unavailable, NIH Form 2803-1 will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside the NIH without an executed MTA or CTA.

End of study procedures: Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

Loss or destruction of samples: If a major breach occurs in the tracking and storage of samples, the IRB will be notified.

9.0 BIOSTATISTICAL CONSIDERATIONS

9.1 Primary Endpoint

- The best overall response rate includes CR, PR, and PRL and will be assessed per Section 7.0. Safety of duvelisib plus ibrutinib combination

9.2 Secondary Endpoints

- Progression-free survival (time from treatment initiation to progression of disease or death from any cause)
- Overall survival (time from treatment initiation to death from any cause)
- Duration of response (time from initial response to progression of disease)
- Best response
- Safety of duvelisib as monotherapy

9.3 Exploratory Endpoints

- Immune cell profiling at baseline, during combination treatment with ibrutinib plus duvelisib, and during duvelisib monotherapy
- Minimal residual disease by flow cytometry in peripheral blood and/or bone marrow
- Quantification of allele frequency of BTK and PLCG2 mutations (if present at baseline) during treatment
- Targeted or whole exome sequencing of sequential tumor samples to assess clonal evolution.
- Measurement of gene expression in cells or tissues. Techniques frequently used include RNA sequencing, gene expression profiling on microarrays, quantitative RT-PCR, Western blotting, flow cytometry and ELISA assays.
- Measurements of drug concentrations, biologic molecules and disease markers in blood, serum, and plasma.
- Culture of cells from research subjects to investigate molecular disease mechanisms, model host tumor interactions, and to test effect of drugs on cell survival and cellular functions.
- Transplantation of human cells into mice (xenograft model) to study disease biology and to investigate the effect of experimental therapy.
- Modifications of cells using standard expression systems or biologic molecules, e.g. interfering RNA, to investigate the effects of candidate genes on cellular functions.

9.4 Sample Size

There are limited data to estimate the true ORR for patients who have developed *BTK* and/or *PLCG2* mutations and/or disease progression following treatment with ibrutinib. In a retrospective cohort study, patients treated with the PI3K δ inhibitor idelalisib after discontinuing ibrutinib for any reason had an ORR of 46%.³⁸ A retrospective study of the French Innovative Leukemia Organization (FILO) reported an ORR of 72% to idelalisib after ibrutinib discontinuation among 29 CLL patients.³⁹ Neither reported the efficacy of idelalisib for ibrutinib-resistant CLL separately. This study will use a Simon two-stage minimax design to test the null hypothesis (H_0) that the ORR after 6 cycles is $\leq 20\%$. If the true ORR is 40%, the following two-stage design would have a power of 80% with a type 1 error of 0.05.

In the first stage, the study will enroll 18 subjects and assess ORR after 6 cycles. If ≤ 4 subjects achieve a response, the study will stop for futility and H_0 is not rejected. If ≥ 5 subjects achieve a response, the study will proceed to the second stage and enroll an additional 15 subjects for a total of 33 evaluable subjects. The null hypothesis will be rejected if ≥ 11 responses are observed in 33 subjects.

Efficacy and safety will be assessed in the intent-to-treat population defined as eligible subjects who provide written informed consent. Up to 3 additional subjects may be enrolled to account for inadvertent enrollment of ineligible subjects.

9.5 Statistical Methods

The planned analyses will include descriptive statistics on the proportions of overall response. The response probabilities will be estimated using the sample proportions and their inferences including confidence intervals and hypotheses testing will be evaluated using binomial distributions. PFS, OS, and DOR will be analyzed using appropriate nonparametric tools in survival analysis such as Kaplan-Meier estimates taking consideration of random censoring.

In addition, methods based on survival analysis, cumulative incidence rates and other competing risk models will be used to evaluate the effect of treatment. Graphical tools will be used to display the appropriate estimates (i.e. estimated proportions and Kaplan-Meier curves) and their corresponding 95% confidence intervals.

9.6 Study Stopping Rules

The study will be halted pending discussions with Verastem, Inc., the FDA and NIH Intramural IRB regarding safety and the need for protocol revisions if any of the following conditions are met:

- If ≥ 2 DLTs at DL_{-1} per Section 3.0.
- If treatment related serious adverse events (TRSAEs) that occur during the treatment period substantially exceed an anticipated rate.

The following specified TRSAEs determined to be related to treatment will be considered for early stopping of the study:

- Death
- Grade 4 non-hematologic toxicity, except abnormal laboratory values which are not clinically significant or isolated in nature and which resolve within 7 days, including electrolyte abnormalities that respond to medical intervention

The anticipated rate of these specified TRSAEs within the first 6 cycles (completion of primary endpoint) is anticipated to be $\leq 20\%$. Following Geller, *et al.*,⁸⁵ the study's stopping rule is determined by a Bayesian approach. The stopping boundary for an experiment is reached if the Bayesian posterior probability that the true probability of developing one or more of the specified TRSAEs exceeds this benchmark rate of 20% is at least 90%. We take our prior distribution to be a beta distribution so that our prior clinical opinion is worth

approximately 20% of the weight we will place on the new data. This gives prior parameters $(\alpha, \beta) = (1.4, 5.6)$. Hence, in deciding to stop the study, data from the study will dominate over prior opinion. Monitoring TRSAEs will start when the first 3 subjects are evaluable for TRSAEs within the first 6 cycles.

Number of subjects in the experiment	Stop if the number of subjects who have developed any of the specified TRSAEs reaches:
3 - 4	3
5 - 8	4
9 - 12	5
13 - 16	6
17 - 20	7
21 - 24	8
25 - 28	9
29 - 32	10
33	11

The performance of the above stopping rule was investigated by a simulation study. In each simulation run, a study with 33 independent Bernoulli trials was generated, each had a probability p for having TRSAE and $q=1-p$ for not having TRSAE and compared the TRSAE outcomes with the above stopping boundary to determine whether the study was stopped. The simulation was repeated 100,000 times and the proportion of stopped studies computed (i.e. “number of stopped studies”/100,000) which were stopped using the above stopping rule. The following table summarizes the proportions of stopped studies under a number of scenarios for p :

Probability of TRSAE = p	0.1	0.15	0.20	0.25	0.30	0.40
Proportion of Stopped Studies	1%	6%	19%	40%	63%	93%
Average number of subjects	32.7	31.7	29.4	25.8	21.4	13.4
Average number TRSAEs	3.3	4.8	5.9	6.5	6.4	5.4

These results suggest that the study’s stopping rule has a low probability of stopping a study when the proportion of TRSAE is $\leq 20\%$, and the probability of stopping a study is high when the true proportion of TRSAE $> 20\%$. Based on these results, the Bayesian stopping rule has satisfactory statistical properties.

9.7 Off Study Criteria

Subjects will be taken off study for:

- Subject choice to withdraw from the study
- Lost to follow-up
- Death
- Study termination

When a subject withdraws from the study, the reason for withdrawal must be documented in source documents. Efforts will be made to obtain partial withdrawal of consent in order to continue to collect survival data on all subjects who were enrolled in the study.

When a subject is lost to follow-up, efforts will be made by the study site personnel to contact the subject and determine the reason for study discontinuation.

Completion of the study: Subjects will be followed indefinitely until an off study criterion is met or the study is closed to further follow up care. Once study participation is complete, the subject will be referred back to his or her referring physician for consideration of standard therapy or evaluated for eligibility for other NIH protocols.

10.0 SAFETY ASSESSMENT AND MONITORING

Principal Investigator (PI): Accrual, efficacy and safety data will be monitored by the PI Clare Sun, M.D., and by the accountable and medically responsible investigator, Adrian Wiestner, M.D., Ph.D.

NIH Intramural IRB: Prior to implementation of this study, the protocol and the proposed patient consent and assent forms will be reviewed and approved by the properly constituted Institutional Review Board (IRB) operating according to 45 CFR 46. Quality assurance and control monitoring will be consistent with the NHLBI Division of Intramural Research Clinical Research Quality Assurance and Quality Control Policy. Accrual and safety data will also be monitored and reviewed annually by the IRB.

NHLBI DSMB: The NHLBI Data And Safety Monitoring Board (DSMB) will review the protocol, progress report, accrual, efficacy and safety data at six- or twelve-month intervals as scheduled. All AEs observed during the clinical trial as detailed in Section 10.3.4 will be reported to the DSMB at the regularly scheduled DSMB meeting. The DSMB may recommend early termination of the study for considerations of safety and efficacy.

Verastem, Inc.: Verastem will approve all amendments to the protocol or informed consent prior to submission to the IRB so long as the protocol is open to accrual or sample and/or data analysis continues. An annual progress report, any amendments to the protocol, and any change in the status of the protocol will be forwarded to Verastem, Inc.

10.1 Assessment of Safety

10.1.1 Severity

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized to describe the severity of AEs (Table 5).

Table 5. Adverse Event Grade (Severity) Scale

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL ^A
3	Severe or medically significant	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL ^B
4	Life-threatening	Urgent intervention indicated
5	Death related to AE	Death related to AE

^A Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^B Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.1.2 Causality Assessments

The following general guideline will be followed:

Unrelated	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
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Unlikely to be Related:	A temporal sequence with the onset of the adverse event and administration of the investigational product is improbable, but not impossible. Concurrent or underlying disease, or the use of other drugs or procedures provide plausible explanations for the adverse event.
Possibly Related	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the adverse event could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible adverse event causes.
Probably Related:	There is a clinically plausible time sequence between onset of the adverse event and administration of the investigational product, and the adverse event is unlikely to be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Clinical response to withdrawal of the investigational product may indicate the adverse event is probably related. <u>Rechallenge with the investigational drug is not required.</u>
Definitely Related	The AE is clearly related to use of the investigational product.

10.1.3 Pregnancy

A subject must immediately inform the Investigator if the subject or subject's partner becomes pregnant from the time of consent to 30 days after the last dose of study drug(s). Any female subjects receiving study drug(s) who become pregnant must immediately and permanently discontinue study drug(s). The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Although pregnancy itself is not regarded as an AE unless there is cause to believe that the study intervention may have interfered with the effectiveness of contraceptive medication or if the outcome of pregnancy meets SAE criteria (miscarriage or congenital anomaly/birth defect, etc.), in which case it should be reported in the same manner and timelines as an SAE, the outcome will need to be documented. Any SAEs associated with pregnancy (e.g. congenital abnormalities/birth defects/spontaneous miscarriage or any other serious events) must additionally be reported. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the in-utero exposure to the study intervention should also be reported as an SAE. Hospitalization for normal delivery of a healthy newborn is not an SAE. Consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested. Subjects will be followed for disease progression and survival until they meet off study criteria in Section 9.7.

Any pregnancy must be reported to Verastem, Inc. within 24 hours of the Investigator's knowledge of the pregnancy using a Pregnancy Report Form. The Investigator will observe the pregnant woman until completion of the pregnancy and must notify Verastem, Inc. of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome using a Pregnancy Outcome Form. This notification includes pregnancies resulting in live, normal births.

10.2 Documentation, Data Collection, and Reporting

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded in the patient's medical record. Each AE/SAE is to be evaluated for duration, severity, seriousness, and causal relationship to the study drugs. The action taken with study drug and the outcome must also be recorded.

Hospitalizations for elective surgery or other medical procedures that are not related to a TEAE are not considered SAEs. Hospitalization, which in the opinion of the Investigator, is unrelated to the study intervention, and due to purely non-medical circumstances (e.g., respite care, lack of a caretaker at home, lack

of transportation home) are also not considered to be SAEs. Progressive Disease (PD) under study (including signs and symptoms of progression) if documented by use of appropriate methods, should not be reported as an SAE unless the outcome of the PD is fatal during the study or within the safety reporting period. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event should be reported using the term "disease progression" with a Common Terminology Criteria for Adverse Events (CTCAE) severity of Grade 5. Death should not be reported as an SAE. The primary reason for a subject's death should be reported as an SAE, with death reported as the outcome.

The following AEs will be recorded in the patient's medical record but not captured in the database:

- Laboratory values that do not result in discontinuation from the study, are not deemed to be clinically significant, or do not require treatment or therapeutic intervention.
- Grade 1 AEs

All other AEs/SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. AEs will be followed to adequate resolution or stability.

10.3 Reporting Period for AEs

The AE reporting period for this study begins when the patient provides written informed consent and ends with the safety follow-up visit. If an SAE is present at the safety follow-up visit or within 30 days of the last dose of study drug (whichever is later), it should be followed to resolution or until the Investigator assesses the subject as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

10.4 FDA, NIH IRB, and CD Reporting

10.4.1 NIH Intramural IRB reporting

- **Expedited Reporting**

- Events requiring expedited reporting will be submitted to the IRB per Policy 801 "Reporting Research Events".

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- **Reports to the IRB at the time of Continuing Review:**

- The PI or designee will refer to HRPP Policy 801 "Reporting Research Events" to determine IRB reporting requirements.

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- **Reports to the CD:**

- The PI or designee will refer to NHLBI DIR Policy to determine CD reporting requirements and timelines.

10.5 Safety Reporting to the Pharmaceutical Collaborator

All events listed below concerning the Verastem, Inc. product must be reported within 24 hours of knowledge of the event or within the defined timeframe to Verastem, Inc. Safety and Pharmacovigilance (email: rtpsafety@ppdi.com, facsimile: 888-529-3580).

- All SAEs regardless of attribution

- Any Safety Information including, but not limited to:
 - Pregnancies including partner pregnancies
 - Breastfeeding
 - Overdose
 - Transmission of an infectious agent through contamination of a Verastem product
- Copies of any correspondence or telephone conversation logs with the applicable Regulatory Authorities regarding all SAEs, regardless of attribution, within a reasonable time frame

The Investigator will provide additional information to Verastem, Inc. about SAEs or Safety Information upon request.

10.6 FDA Regulatory Requirements (Waived)

An IND application with the FDA is not required for this study. The proposed research with duvelisib and ibrutinib meets the exemption requirements noted in 21 CFR 312.2, specifically:

1. The drug products are lawfully marketed in the United States.
2. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
5. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
6. The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

10.7 Considerations for Other Reportable Events

Unanticipated Problems

Definition:

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

Reporting:

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801 and to the NHLBI Clinical Director per NHLBI guidelines.

Protocol Deviations

NIH Definition:

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

Reporting:

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations to the NIH Institutional Review Board as per Policy 801 and to the NHLBI Clinical Director per NHLBI guidelines.

11.0 BIOSPECIMEN AND DATA MANAGEMENT PLAN

11.1 Data Management

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The PI, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts to ensure that data is verifiable and evaluable. Data will be abstracted from Clinical Center progress notes and investigations as well as from outside medical records. Laboratory data from NIH will be imported electronically from CRIS into an in-house clinical trial database. Laboratory values from outside physicians will be entered into the system.

Research data will be prospectively collected by authorized personnel and entered into an NHLBI, 21 CFR 11 compliant, database which will consist of the study specific set of electronic CRFs (e-CRFs) used for capturing, managing and reporting clinical research data.

We will maintain the confidentiality of identifiable private information collected in this Clinical Trial and protect the privacy of the individual human subjects. Primary data containing individually identifiable information obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH information security standards. Neither individual personal identifiers nor the key linking coded data to individuals will be released to third parties including Verastem, Inc. without prior IRB approval.

11.2 Data Sharing and Future Use of Data

De-identified human data generated for use in future and ongoing research will be shared through a NIH-funded or approved repository (ClinicalTrials.gov) and BTRIS. At the completion of data analysis, data will be submitted to ClinicalTrials.gov either before publication or at the time of publication or shortly thereafter.

Research data may be shared with qualified non-collaborator recipients following publication of the primary research results after removal of PII. Refusal of a research subject participant to permit future use of data--other than required in the protocol --will be honored. Limitations in data sharing and future use of data due to

contractual obligations (e.g., CRADAs) or intellectual property proceedings (such as patent filings) will be honored.

11.3 Future Use of Biospecimens

Following analyses of biospecimens for primary research purposes, remaining samples suitable for future research will be stored in manner that conforms with DIR policy (such as BSI) or in a publicly accessible research biospecimen repository following IRB approval. Biospecimens may be destroyed only when permitted by the clinical director and the IRB.

Any future research use of biospecimens not defined in the protocol in which NHLBI investigators are engaged in research (e.g., they are undertaking research activities and hold the key that identifies research subjects) requires IRB review and approval. Coded biospecimens (NHLBI investigators hold the key that identifies research subjects) to be shared outside of NIH for future research use requires an executed transfer agreement and may require IRB approval if results will be returned and re-identified. Unlinked biospecimens (no key to identify research subjects exists) to be shared outside of NIH for future research use requires an executed transfer agreement. Refusal of a research subject participant to allow for future use of identifiable biospecimens--other than required in the protocol or for appropriate regulatory purposes --will be honored.

11.4 Clinical Monitoring

As per ICH-GCP 5.18 and FDA 21 CFR 312.5 clinical protocols are required to be adequately monitored by the study sponsor. The monitoring of this study will be conducted by Clinical Research Associates (CRAs)/Monitors employed by an independent contract organization working under an agreement with NHLBI to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent form (ICF) and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information with individual subjects' records and source documents (subject's charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections-OHRP) and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit. The investigator (and/or designee) will make study documents (e.g., consent forms and pertinent hospital or clinical records readily available for inspection by the local IRB, the site monitors, and the NHLBI staff for confirmation of the study data.

12.0 HUMAN SUBJECT PROTECTION

The investigator(s) accept their responsibilities for protecting the rights and welfare of human research subjects and will permit, with reasonable advance notice and at reasonable times, the designated research monitors to monitor the conduct of the research, as well as to audit source documents to the extent necessary to verify compliance with FDA Good Clinical Practice and the approved protocol.

12.1 Rationale for Subject Selection

12.1.1 Predicted Distribution by Gender, Age and Race

CLL is a rare neoplasm that comprises a substantial proportion of all leukemia in middle-aged persons and is the most common type among elderly persons in western populations. Epidemiologic studies suggest that distribution by gender will be 66% males and 33% females.¹³ CLL is more common in Caucasian and African-American but rare in Hispanics and very rare in the Asian population. This study will be open to all patients

who fit the inclusion criteria and provide informed consent to protocol participation. We would predict that distribution should be comparable to that seen on the NHLBI Hematology Branch screening protocol as follows:

- by gender: 33% females; 66% males
- by age: ages 23-79, median 60
- by race: 2% Asian, 11% Black, 8% Hispanic, 79% White

12.1.2 Special Populations:

Justification for exclusion of children: CLL is uncommon in patients less than 45 years of age and is virtually unknown in patients less than 20 years of age. At the time of diagnosis, more than 95% of patients are 45 years old and above.⁸⁶ CLL may also be, biologically, a different disease in children. Ibrutinib has not been studied in human subjects under 18 years of age. For these reasons, individuals < 18 years old have been excluded from protocol participation.

Justification for exclusion of pregnant women: There are no clinical studies that were done on pregnant women, and it is unknown whether duvelisib, ibrutinib, or their metabolites are excreted in human milk. In addition, it is highly unlikely that a woman of pre-menopausal age will present with CLL because it is a malignancy of B cells that predominantly affects the elderly population. Diagnosis is typically made in adults over the age of 50 and more than half of the people with CLL are over the age of 70.

Justification for exclusion of patients with impaired hepatic or renal function: No specific clinical studies have been conducted to date in patients with impaired hepatic or renal function. To minimize risks, patients enrolled must have adequate hepatic and renal function as defined in eligibility and exclusion criteria.

Justification for exclusion of cognitively impaired subjects

Cognitively impaired and institutionalized persons will not participate in this study. Subjects must be able to provide informed consent, and understand and comply with the treatment plan and follow-up.

Recruitment: The study will be listed on the ClinicalTrials.gov, Clinical Center Research Studies, and the NHLBI patient recruitment websites. The NHLBI DIR Patient Recruitment Office (PRO) will work with the Investigator to ensure accrual goals are being met. All recruitment materials and tools will use IRB-approved language and information to include standard recruitment contacts.

- Anticipated accrual rate: approximately 12 subjects per year
- Anticipated number of sites and participants to be enrolled from the U.S. and outside the U.S.: 1
- Source of participants (e.g., inpatient hospital setting, outpatient clinics, student health service, or general public): outpatient clinic, general public, physician referrals
- Medical records provided from outside referral sources will be reviewed to determine possible eligibility
- A Strategic Recruitment Plan (SRP) has been developed in conjunction with the NHLBI Patient Recruitment Office. Recruitment strategies that will be ongoing throughout recruitment period of trial may include 1) distribution of a recruitment flyer in the NIH campus, patient advocacy organizations and the community; 2) updating study information on clinicaltrials.gov, NIH Search the Studies, and a dedicated recruitment page on the Clinical Center Office of Patient Recruitment website; 3) the use of ResearchMatch for identification of study candidates; 4) promoting the study on the official NIH social media account with IRB approved language and images; 5) distribution of a recruitment information on NIH listservs; and 7) distribution of a physician-to-physician letter to local hematologists/oncologists.

Payment for participation: \$0 – Subjects will not be compensated for their participation in this study. There is no payment for the blood samples obtained for research.

Reimbursement for protocol participation travel, food, and lodging will be consistent with NHLBI DIR Travel and Lodging Compensation of Clinical Research Subjects policy or institutional guidelines.

For travel from home: Travel from home for the first NIH visit will not be reimbursable. If the patient consents to protocol participation travel home following the first visit will be reimbursable. Subjects will be reimbursed 100% of government rate for travel once the subject has been determined eligible to participate and signs consent.

Competition with other Branch protocols: The study is the only active treatment protocol for subjects who develop *BTK* and/or *PLCG2* mutations or progressive disease on ibrutinib. There will be little competition with existing NHLBI protocols.

12.2 Risks in Relation to Benefit

The benefits to the subject could be a reduction or a disappearance of CLL, resulting in improved quality of life, decreased susceptibility to infections, and foremost, significant improvement in survival time. Potentially, treatment with other therapies could also be avoided or postponed.

12.3 Informed Consent Process and Procedures

The investigational nature and research objectives of this trial, the procedure and its attendant risks and discomforts will be carefully explained to the subject and a signed informed consent document will be obtained prior to entry onto this study.

At any time during participation in the protocol, should new information become available relating to risks, adverse events, or toxicities, this information will be provided orally or in writing to all enrolled or prospective patient participants. Documentation will be provided to the IRB and if necessary the informed consent amended to reflect relevant information.

12.4 Conflict of Interest

Verastem, Inc. is providing duvelisib for this study to NIH without charge. No NIH investigator involved in this study receives any payment or other benefits from Verastem, Inc.. The principal investigator assures that each associate investigator received a copy of the NIH's Guide to preventing conflict of interest. No members of the research team reported a potential conflict of interest.

12.5 Technical Transfer Agreements

The protocol has an associated CRADA: between NHLBI and Verastem, Inc.

12.6 Protocol Amendments

Per the IST Agreement, any amendments to the protocol or informed consent form must be sent to Verastem, Inc. for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

12.7 Publication Policy

Per the IST Agreement, the Investigator is required to submit to Verastem, Inc. a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. If safety information is contained within the document, the Investigator shall provide details regarding the safety events (patient identifier, reported term and causality) to Verastem, Inc. Verastem, Inc. may provide

scientific comments and suggestions understanding that the Investigator has sole editorial responsibility, and retains the authority to make the final determination on whether or not to incorporate Verastem, Inc. comments or requests for additional information.

13.0 PHARMACEUTICALS

13.1 Duvelisib

Product Description: Duvelisib is a synthetic small molecule compound manufactured in high enantiomeric and chemical purity. The duvelisib drug substance is a freebase, hydrate (hydration can vary with humidity), white-to-off-white solid, and is chemically stable under the recommended storage condition of 2 to 30°C.

Formulation, Packaging, and Storage: The duvelisib drug product is supplied as capsules in 3 strengths for oral administration: 5 mg, 15 mg and 25 mg. The drug product consists of a blend of duvelisib drug substance formulated with compendial (USP, Ph. Eur., JP) excipients. The gelatin capsule is not compendial, however the capsule components comply with compendial requirements. The drug product is provided as a white powder encapsulated in corresponding capsule sizes and colors. Capsules are packaged in opaque high-density polyethylene (HDPE) bottles with induction sealed child resistant caps or thermoform blister strips with push-through lidding packaged into wallets.

The drug product bottles or blister strips should be stored at room temperature (15 to 30°C). The capsules are intended for oral administration. Caution is required when handling duvelisib. Personnel dispensing duvelisib should follow standard procedures for the handling of investigational drugs, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, the individual should be treated for physical exposure (skin washing) or inhalation (move to fresh air, as necessary), and, if needed, seek medical advice. When duvelisib capsules are dispensed for self-administration, they should only be handled by the study subject. After handling capsules, the subject should wash his or her hands thoroughly. If someone who is not enrolled in a duvelisib clinical trial swallows a capsule or inhales drug powder from a broken capsule, he or she should contact the relevant Investigator to determine whether safety monitoring is necessary. The Investigator should report the incident to Verastem, Inc. Capsules should always be stored in the container provided to the study subject.

Dosage and Administration: Refer to Section 5.1.

Overdose: In the case of overdose, supportive care should be administered as indicated.

Supply: The drug product duvelisib is manufactured and supplied by Verastem, Inc.

Shipping: National Institutes of Health
Investigational Drug Management and Research Section
Clinical Center Pharmacy Department, Room 1C230
10 Center Drive, MSC 1196, Building 10
Bethesda, Maryland 20892-1196

13.2 Ibrutinib

Product Description: Ibrutinib is commercially available. Note for more detailed and comprehensive background information please refer to the ibrutinib Package Insert. Chemical name of ibrutinib is PCI-32765-00, which is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one. PCI-32765-00 is a white to off-white crystalline solid, and given as an oral formulation containing micronized PCI-32765-00.

Formulation, Packaging, and Storage: Ibrutinib is provided as 140 mg white opaque capsules or tablets in 4 strengths: 140 mg, 280 mg, 420 mg, and 560 mg. The capsules are packaged in white HDPE bottles with a child-resistant closure. The tablets are packaged in a carton of one folded blister card containing two 14-count blister strips. Store bottles or tablets at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F).

Dosage and Administration: Refer to Section 5.1.

Overdose: There is no specific experience in the management of ibrutinib overdose in patients. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Closely monitor patients who ingest more than the recommended dosage and provide appropriate supportive treatment.

Supply: Commercially available from the NIH Clinical Center Pharmacy Department.

13.3 Accountability Procedures

Drug accountability records will be maintained for all clinical supplies. All empty and partially used vials and clinical trial supplies will be destroyed locally according to the institution's standard operating procedures for drug destruction. The pharmacy will maintain detailed documentation of the number and identification of vials which are destroyed, and copies of these documents will be provided to the sponsor. Disposition of all unused boxes of study drug will be carried out according to instructions provided by the sponsor at the end of the study after drug accountability is performed by the study monitor.

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APPENDIX A: SCHEDULE OF EVENTS

EVALUATION AND ASSESSMENTS			Screen and Baseline Visit							After C6D28	Progression of Disease	Permanent D/C of Duvelisib *30 days after last dose + 7D
PROTOCOL TIMEPOINT				C1D28	C2D28	C3D28	C4D28	C5D28	C6D28		Unscheduled Visit	
Window +/- days			+/- 4 wks	+/- 7D	+/- 7D	+/- 7D	+/- 7D	+/- 7D	+/- 7D		+/- 15D	
day /month												
Clinical												
Consent			X									
History			X	X	X	X	X	X	X		X	X
Physical Exam			X	X	X	X	X	X	X		X	X
ECOG PS			X	X	X	X	X	X	X		X	X
Concomitant Medication Review			X	X	X	X	X	X	X		X	X
Labs												
HLA Typing			X1									
CBC with Differential			X	X4	X4	X	X	X	X		X	X
Acute Care & Mineral Panel			X	X	X	X	X	X	X		X	X
Tot. protein, Uric Acid, LDH			X	X	X	X	X	X	X		X	X
Hepatic Panel			X	X	X	X	X	X	X		X	X
Reticulocyte Count			X	X	X	X	X	X	X		X	X
PT, PTT			X									
SPEP with IFE			X									
SFL with qIG			X			X			X		X	
CRP			X	X	X	X	X	X	X		X	
β2 Microglobulin			X	X	X	X	X	X	X		X	X
Haptoglobin			X	X	X	X	X	X	X		X	X
DAT			X	X	X	X	X	X	X		X	X
Iron studies (ferritin, transferrin, iron)			X									
Folate, Vit B12			X									
Thyroid function panel (thyroid stimulating hormone, free T4, T3)			X									
Pregnancy test			X3									
Lymphocyte phenotyping (T, B, NK)			X			X			X		X	X
IGHV mutation analysis (blood or BM?)			X1									
Peripheral blood flow cytometry for CLL			X						X		X7	X

APPENDIX B: CYP3A INHIBITORS, INDUCERS, AND SUBSTRATES

Medications or Foods Known to Inhibit CYP3A

The following list provides medications or foods known to induce or inhibit CYP3A activity. Note that this is not a comprehensive list of all medications or foods which may modulate CYP3A activity. Additional information can be found at:

<https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>

Note: Subjects receiving duvelisib are prohibited from concomitant use of medications or foods that are known to be strong inhibitors or inducers of CYP3A.

Table 7. Classification of In Vivo Inhibitors of CYP3A

Strong Inhibitors¹	Moderate inhibitors²	Weak inhibitors³
Boceprevir, clarithromycin, conivaptan, grapefruit juice ⁴ , indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil ⁵ nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice ⁴ , imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo ⁶ , goldenseal ⁶ , isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

1. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by ≥ 5 -fold or $> 80\%$ decrease in CL.
2. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold or 50-80% decrease in CL.
3. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold or 20-50% decrease in CL.
4. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
5. Withdrawn from the United States market because of safety reasons.
6. Herbal product.

Medications Known to Induce CYP3A

Table 8. Classification of In Vivo Inducers of CYP3A

Strong Inducers $\geq 80\%$ decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
Avasimibe ¹ , arbamazepine, phenytoin, rifampin, St. John's Wort ^{2,3}	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, Echinacea ³ pioglitazone, prednisone, rufinamide

Abbreviations: AUC: area under the curve; CYP3A: cytochrome P450 3A.

1. Not a marketed drug.
2. The effect of St. John's Wort varies widely and is preparation-dependent.
3. Herbal product.

Medications Known to Be CYP3A Substrates

Known sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic range are listed in

Table . Drugs or foods that are substrates of CYP3A should only be used if medically necessary and therapeutic alternatives do not exist.

Additional information can be found at

- <https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>
- <http://www.pharmacytimes.com/issue/pharmacy/2008/2008-09/2008-09-8687>

Table 9. Cytochrome P450 3A (CYP3A) Substrates

Sensitive CYP3A Substrates	
budesonide buspirone epplerenone eletriptan felodipine fluticasone lovastatin	midazolam saquinavir sildenafil simvastatin triazolam varafenafil
CYP3A Substrates with a Narrow Therapeutic Range	
alfentanil astemizole cisapride cyclosporine diergotamine ergotamine	fentanyl pimozide quinidine sirolimus tacrolimus terfenadine